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CHONDRO-OSTEO-DYSTROPHY OF THE HURLER TYPE (GARGOYLISM). A PATHOLOGICAL STUDY.

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OF the syndromes composing the complicated group of congenital osseous dystrophies, not the least remarkable is that which has as its cardinal features mental deficiency, dwarfism, deformity of the limbs, corneal opacities and enlargement of the liver and spleen.

This bizarre combination of clinical signs was first described by Gertrud Hurler, who in 1919 recognized that the features of her two cases represented a unit syndrome quite unlike anything hitherto described. Her account was soon followed by a number of others, often described as isolated instances of unusual clinical cases; but early in 1936 a new impetus to the study of the condition was given by Ellis, Sheldon and Capon, who reviewed the records of ten cases collected from the literature, to which they were able to add seven personally observed. On account of the large head, grotesque inhuman facies and deformed limbs, they suggested for this form of chondro-osteo-dystrophy the name gargoylism.

In the absence of post-mortem material these authors were unable to contribute to the pathology of the condition; but they noted that the microscopical findings in Hurler's first case, subsequently investigated by Tuthill (1934), were such as to suggest the possibility of a general disturbance of lipoid metabolism.

Our present communication is concerned with the pathological investigation of the nervous system and certain visceral organs of two cases. The first of these was a male patient who was shown at the Royal Society of Medicine in 1921 by Jewesbury and Spence under the heading "Acrocephaly with other Congenital Deformities"; the second case was the elder of two sisters, the younger of whom had been the first case described in the series recorded by Ellis and his co-workers.

In both our cases evidence was found not only that this dystrophy

was closely allied to the diseases of metabolism in which there is storage of lipoid in the reticulo-endothelial system—the so-called xanthomatoses or lipoidoses—but that, as Tuthill surmised, the histological appearances in the nervous system were very similar to those found in amaurotic family idiocy.

Before describing the pathological aspect of our two cases, it may be useful to review the salient clinical features of the disease.

Bone changes.—Skull: Hydrocephalus has been noted in several cases, but, even when this is not present, the cranium is invariably enlarged, and in shape brachycephalic, scaphocephalic, acrocephalic or mildly oxycephalic. Prominence of the frontal bones and supra-orbital ridges, lateral bossing of the temporal bones and prominent bony ridges in the neighbourhood of the sutures have been described. In three cases there was distension of the frontal veins. The facial portion of the skull may be small in proportion to the large cranial vault, though more often the face is described as being broad and full. The bridge of the nose is almost invariably depressed, and increased inter-orbital breadth is also a characteristic feature. The inferior maxilla is usually strongly developed, while the frequent disclosure by radiography of a marked enlargement of the pituitary fossa is of considerable interest.

Vertebral column: Nearly all subjects present a marked shortening of the cervical spine so that the massive head appears to sit almost directly on the shoulders. With one or two exceptions, all the recorded cases have shown an obvious degree of kyphosis, usually dorsilumbar, but not associated with scoliosis. Spina bifida may be present. The radiological appearances bear a close though not identical resemblance to those found in osteochondropathia multiplex. In both diseases there may be platyspondylosis; irregularity of alignment with backward projection of a lower dorsal or lumbar vertebra; and, very characteristically, a hook line projection on the anterior aspect of the body of one of the upper lumbar vertebræ.

Thorax: The clavicles may be massive and thick. Deformity of the thoracic cage, though never so gross as in Morquio's disease (1929), is usually present. "Trichterbrust," pectus carinatum, Harrison's sulcus, rachitic flare, beading, and expansion of the ribs at their sternal ends have all been described.

Limbs: A certain degree of micromelia is usually present, the long bones being not only shorter but thicker than normal. More characteristic, however, is the limitation of movement, which has its maximum development in the digital joints. The fingers are short and clumsy,

and usually show some degree of flexion. In advanced cases flexion at the terminal joints is marked, the finger ends presenting a peculiar hook-like appearance. This condition of claw hand must be considered one of the most distinctive features of the syndrome. The hands are described as being broad and paw-like. The thumb and metacarpophalangeal joints may show no restriction of movement.

Shortening and deformity is much less evident in the lower limbs, but there is usually limitation of movement at the knees, and genu valgum and coxa vara have both been described. Radiographic examination of the limbs shows poorly developed glenoid fossæ and acetabula, with flattened irregular heads to the humeri and femora, and short broad metacarpals and phalanges. Delayed epiphyseal development has been noted.

Teeth.—Various irregularities and defects are found. The incisors may be spaced, obliquely placed, massive or hypoplastic, and sometimes show crescent-shaped notches on their free borders.

Eyes.—Slight ptosis, large thickened lids and internal strabismus have been reported, but the most constant abnormality, and one which must be given a high diagnostic value, is congenital clouding of the cornea. When present the clouding is uniform in both eyes and, as might be expected, its effect on vision varies with its degree. Appearing first as a diffuse haziness which causes little interference with vision, with the passage of time it becomes more pronounced until the cornea acquires an opaque milkiness which reduces visual acuity to perception of light only. The condition is said to be caused by the presence of multiple opacities scattered principally in the deeper layers of the cornea. The pupillary reflexes do not appear to be interfered with. In more than one case an abnormally large cornea has been noted. Another change which may ultimately occur is buphthalmos. In a moderate degree it existed in the terminal stages of the illness of our patient M., and it was a marked feature in two siblings reported by Davis and Currier (1934). Although these authors regarded their cases as examples of Morquio's disease, and although corneal opacities were not specifically referred to, an analysis of their findings leaves little room for doubt that they were in reality dealing with the syndrome now under discussion.

Visceral organs.—Enlargement of both the liver and spleen has been noted on at least ten occasions, while enlargement of one organ alone—usually the liver—occurs almost as frequently. In our two cases, verified by post-mortem examination, neither of these two organs was enlarged.

Facies.—In certain respects the facial appearance resembles both that of the congenital syphilitic and that of the cretin. Even in infancy the features are peculiarly ugly and unchildlike. Congenital syphilis is suggested by the corneal opacity, the snub nose and, when present, the notched incisors; while the full rounded broad cheeks, thick everted lips and a partially open mouth are reminiscent of cretinism. In several of the recorded cases competent observers have made a diagnosis of hypothyroidism.

In nearly every case the eyebrows have been described as coarse and heavy, often contrasting with the hair on the scalp. On the latter it may be fine and silky, or coarse and wiry, but seldom scanty. The ears are usually low and obliquely placed.

Tongue.—The tongue is usually described as being large and at times protruding, as in the second case reported by Hurler (1919). In the case, the clinical history of which is given at length in this paper, the tongue was not only large but exhibited fissuration and prominent papillæ very much like that of the Mongol.

Skin.—On the face the skin has been described as soft and rosy, while on the body it may be pale, muddy, sallow, and dry. Hurler noted that the skin on the chest could be lifted up in folds, and that cushions of fat were present in the mammary region and on the abdominal walls. It is perhaps more than a coincidence that in several cases the weight at birth has much exceeded the normal. A marked lanugo may be found on the face, trunk and limbs. In one case a marked degree of hypertrichosis was present on the lower limbs.

Muscular system.—Though actual wasting has not been observed, the musculature is usually poorly developed, especially that of the abdomen. A marked degree of abdominal distension is a very frequent finding, and, in two cases, diastasis of the recti was present. Umbilical, and, less frequently, inguinal herniæ are also characteristic features.

Nervous system.—No gross abnormality has been recorded except in the cases reported by Davis and Currier. Their two siblings developed optic atrophy, and, in the elder boy, an encephalogram showed symmetrical dilatation of the lateral ventricles with slight enlargement of the third ventricle. Several of the cases reported could stand only with assistance, but it does not appear that any true motor paralysis exists.

Mental state.—From the published reports it is a little difficult to assess the exact mental status of the recorded cases, but as a rule some degree of mental retardation is present. The majority of the subjects

have been young children and few have progressed beyond the stage of low grade imbecility. Speech was either not acquired at all, or was limited to the utterance of a few words. Habits of cleanliness were acquired only by a few. Of the seven cases described by Ellis, Sheldon and Capon (1936), their first, a female dwarf of 18, was the most intelligent. She learnt to speak a few words, to understand simple requests, and to acquire clean habits. The same authors refer to the possibility of mental regression, and this is borne out by the clinical history of our patient. In 1921, at the age of $5\frac{1}{2}$ years, he was clean in his habits, could speak, and although his intelligence was limited, was by no means an idiot. Fifteen years later he had sunk to the lowest grade of amentia, and was in fact a typical idiot, noisy, resistive and completely inaccessible.

These patients are for the most part of friendly disposition, docile and obedient and usually inactive, being content to lie quietly in bed. In the majority the ability to walk is acquired late. In the two cases reported by Davis and Currier "Intelligence seemed to be unimpaired," but we are not told whether their mental state was investigated by the application of special tests. Nevertheless, the possibility of normal mental development has to be envisaged. Nonne (1924) refers to three sisters who were intelligent, and, through the kindness of Dr. Orr-Ewing of Bristol, one of us has had the opportunity of examining two brothers whose degree of mental retardation was so slight as to be almost completely masked by their specious brightness : yet otherwise they were both extremely typical gargoyles.

Other features.—Some stress is laid by Ellis and his co-workers on the presence of rhinitis, but it is by no means constant. For the most part biochemical investigations have proved negative; only in one case has the possibility of defective liver function been suggested by a slightly abnormal lævulose tolerance test and a high blood glycogen. The formed elements of the blood show no abnormality. Sexual development appears either to remain infantile, or be in harmony with the stage of physical development reached. Extreme sexual infantilism was however present in the first case of the series reported by Ellis and his co-workers. The heart, lungs and urine are usually normal, and no abnormality of thyroid, thymus or lymphatic glands has been detected during life. In Case 2 of this paper a marked degree of mitral stenosis was present. Constipation does not appear to be a prominent feature, but a tendency to respiratory infection is fairly common.

Family history.—Almost invariably the parents are healthy and consanguinity is exceptional.

Report of Cases.

Case 1.—S. M., aged 19, was admitted to Leavesden Hospital on November 2, 1934.

Family history.—Apart from a history of nervous breakdown in the father, a railway porter, the family history was satisfactory. A blood Wassermann reaction made on the parents was negative in each instance.

Past history.—The patient is the elder of two male children, the second, aged 15, being normal and in employment as an office boy. During pregnancy the mother endured mental stress, and there was protracted pressure and asphyxia at the birth of the patient, which was aided by instrumental delivery. At birth he weighed 12 lb., and was said to have had a repulsive appearance, being born with a deformed skull and a film over both eyes. Teething was normal but there was considerable delay in learning to walk and talk, neither function being acquired until after the fourth year. Speech never went further than the acquisition of the language of infancy. He acquired cleanliness in habits and was able to feed himself.

In infancy he suffered from measles, and received out-patient treatment for his eye condition. This, however, did not prevent him from seeing fairly well, as the mother stated that he ran about without bumping into things. He was never able to use his right upper limb to the same extent as his left. He was a heavy child, and, on the supposition that he suffered from thyroid deficiency, thyroid extract was administered over a period of two years. No apparent benefit was observed, and the mother finally discontinued the treatment because she thought it was making him violent.

When in his 5th year he was shown by Jewesbury and Spence (1921) at the Royal Society of Medicine, Section for the Study of Disease in Children. He was then of normal weight and height, but presented a curious appearance. His face was "full-moon" in shape, the bridge of the nose depressed, the eyeballs prominent, the head brachycephalic, the corneæ cloudy, and the hands in a condition of "claw fingers." Examination of the blood, urine and cerebrospinal fluid gave negative results. Sugar tolerance was normal. On radiographic examination the pituitary fossa was noted to be twice its normal length but without evidence of erosion or absorption. The metacarpals and phalangeal bones were irregular in shape, the proximal phalanges tending to be cone-shaped and the terminal phalanges being smaller than normal. Radiographic examination of the other parts of the skeleton failed to reveal further abnormalities.

In 1922, when 7 years of age, he was examined and deemed to be mentally defective. He was admitted to a special school, but made only twenty-four attendances. In conduct he was restless and spiteful, never still, and constantly interfering with other children. He made no educational progress whatever, and, when re-examined in January, 1923, was graded as imbecile (fig. 1). Thereafter he remained at home, showing little change until his 17th year, when it was noticed that he was becoming weak on his legs. About this time he fell on the back of his head, and was apparently unconscious for about a

quarter of an hour. According to the statement of his mother, within three days of this accident he was unable to walk at all and became almost completely blind. After a period of institutional care in St. John's Hospital he was certified under the Mental Deficiency Acts.

Examination.—The patient is dwarfed in stature, with cretinoid features and generally repulsive in appearance. Height, 4 ft. 2 in.; weight, 5 st. The head is rounded with flattening in the occipital region, large in proportion to the size of the body, with closed fontanelles and no evidence of bossing. It has the following measurements: Height, 158 mm.; length, 183 mm.; breadth, 153 mm.; circumference, 56·7 cm.; cephalic index, 84. The hair on the scalp is coarse and dry, dark in colour and sparse. The eyebrows are heavy and strongly arched. The eyes are large, prominent, widely set and show a moderate degree of buphthalmos. On both sides the cornea is a milky white colour, the degree of clouding being evenly distributed and diffuse, but not sufficiently marked to obscure completely the outline of the blue iris beneath. The pupils react a little sluggishly to light and visual acuity appears to be much reduced. It was not possible to see the discs.

The nose is flat and broad with depressed bridge and nostrils which look forwards as well as downwards. There is no nasal discharge.

The lips are thick and everted, the tongue large and protruding with well-marked circumvallate papillæ and some degree of fissuration, though less pronounced than that seen in a Mongol. The palate is highly arched; the upper central incisors show a trace of notching at their free edges but are not peg-shaped, the condition of the permanent teeth is fair and the lower jaw fully developed.

The face is large and broad with pale flabby cheeks and large ears set rather low.

The neck is remarkably short and thick, the thorax wide, with flaring of the costal margin: a marked Harrison's sulcus is present.

The abdomen is large, protuberant, and shows the presence of a small umbilical hernia.

The skin of the trunk is coarse and dry with a marked excess of coarse hair on the buttocks and legs.

Sexual development exceeds the normal.

Both upper limbs are short with limitation of movement at the elbows and joints of the fingers. The digits are short, especially their terminal phalanges, and the terminal interphalangeal joints are acutely flexed in a remarkable hook-like way. The right thumb is flexed, the left extended. The lower limbs are in proportion to the size of the trunk; they are extended and show a moderate degree of rigidity at knee and hip joints; the feet and toes are large in proportion to the size of the legs but show no abnormality in posture. No kyphosis is present.

The thyroid, liver and spleen are not palpable, and examination of the lungs and heart reveals no abnormality. Pulse 108, blood-pressure 136/50 mm. Urine normal. The Wassermann and Meinicke reactions are negative.

Abdominal reflexes present. Plantars: flexor response. Arm and knee jerks brisk. He is unable to sit, stand, or walk, but retains considerable power in his limbs, clutching at people within reach with a surprisingly firm hold.

Progress.—The patient was confined to a chair from which he made no effort to move, or to interest himself in his surroundings. He was extremely resistive, difficult to feed (spoon feeding usually occupied twenty minutes), and faulty in habits. He often uttered a plaintive harsh cry, but was not observed to shed tears. "Bread," "Mummy," and "Daddy," were the only words he was heard to say. When asleep his breathing was always noisy and snoring.

One month after admission he developed an attack of bronchitis, and the thyroid treatment which had been commenced on his admission was discontinued. His illness lasted a fortnight and he appeared to be making a good recovery. On the evening of April 26, 1935, however, he suddenly collapsed in his chair, and all efforts to revive him proved unsuccessful.

Post-mortem examination.—An autopsy performed sixteen hours after death revealed large persistent thymus; thyroid of normal size, firm and with well-defined isthmus; heart small but otherwise normal; bilateral pulmonary congestion; liver weight 960 g., capsule thickened and marked decrease in bulk of left lobe; on section, slight fatty change. Spleen, weight 100 g., of normal consistence and appearance. Kidneys and suprarenal glands normal. The pituitary gland lay in a much widened sella turcica, and was enlarged to almost twice the normal size, both lobes sharing in this enlargement.

The inner and outer tables of the calvarium were thickened and dense, with obliteration of the diploë. The metopic suture was not closed throughout its whole length. The brain was of normal consistence, and, after fixation in 10 per cent. formol saline weighed 1043 g. Right cerebral hemisphere 495 g. Left cerebral hemisphere 393 g. Cerebellum 155 g. The cerebral hemispheres were asymmetrical; the left was broader and flatter than the right, and had on its surface a large area of cortical atrophy covered by thickened and opaque pia-arachnoid. The lesion occupied the stem of the Sylvian fissure, part of the inferior frontal, and the lower halves of the pre- and post-central gyri.

The right cerebral hemisphere showed two small areas of thickened pia-arachnoid, but without cortical atrophy—one occupying the horizontal ramus of the Sylvian fissure and the other in the prefrontal region. On both hemispheres the convolution pattern was somewhat simple.

On division of the two cerebral hemispheres a condition of unilateral hydrocephalus was revealed. The left lateral ventricle showed a very marked degree of ventricular dilatation affecting all its area. Save for a small area overlying the caudate nucleus there was no evidence of ependymitis. Attached to the choroid plexus in the body of the ventricle was a small, firm, rounded tumour about the size of a hazel nut. From its position it was obvious that the foramen of Monro could not have been blocked. Another tumour occupying the same position, and of the same size, was present on the choroid plexus of the otherwise normal right lateral ventricle. A vertical coronal section

through the left cerebral hemisphere in the plane of the middle commissure showed that the area of softening was sharply confined to the cerebral cortex in the region described above, with, however, marked thinness of the underlying white matter. On this side, too, the basal ganglia were much smaller than on the opposite and normal side.

The cerebellum was symmetrical with a normal fourth ventricle. Both pyramids, especially the left, were poorly developed; the vertebral arteries were large but otherwise normal.

Microscopic examination.—Pituitary: The morphological appearance of the anterior lobe cells suggested a normal gland which had undergone a general cell hyperplasia. There appeared to be a full complement of acidophile and basophile cells, and possibly some increase in the number of chromophobe cells, but differential counts on serial sections were not attempted. The posterior lobe, though large, showed no abnormal structure.

Thyroid: In all sections the appearances were those of a fœtal type of gland, the tissue consisting almost entirely of masses of cells, some solid and others showing a scarcely distinguishable lumen (fig. 2). Here and there colloid, which stained with basic but not acid dyes, could be seen as small droplets. A few vesicles showed almost normal colloid storage. The epithelium tended to be columnar rather than cuboidal, and to desquamate.

Thymus: The normal structure was preserved. Hassall's corpuscles were present.

Suprarenal: No evidence of disease was found.

Tongue: anterior third. The papillæ were hypertrophied and covered by a much thickened and folded epithelium. Some inflammatory infiltration was present in the muscular tissue beneath.

Tumours of choroid plexus: Both tumours consisted of a loose stroma of fibro-myxomatous tissue in which were large quantities of rounded bodies resembling corpora amylacea. The blood-vessels showed thickening of the media and adventitia, and in places there was a cellular infiltration, the cells consisting chiefly of lymphocytes.

Microscopic examination of nervous system.—Celloidin sections of various cerebral convolutions and of the basal ganglia, pons, cerebellum, medulla oblongata and optic nerves were stained with hæmatoxylin-eosin, cresyl violet and Loyez's myelin sheath stain. Frozen sections from various regions were stained with Scharlach R, Nile blue, Bielschowsky's and Holzer's methods. Tissue mordanted in 2 per cent. bichromate of potassium solution was stained by the methods of Marchi and Wolters. For the identification of deposit in certain areas special staining methods were adopted.

Nerve cells: Low power examination of the cerebral cortex showed a considerable disturbance of the cyto-architectonics, the normal columnar arrangement of nerve cells being often lost, and many cells displaying a loss of their normal polarity. The average thickness of the cortical grey matter was slightly less than normal, the reduction being most evident in the supragranular layers.

In the region of the cortical scar on the surface of the left cerebral hemisphere no ganglion cells could be identified. Elsewhere the ganglion cells throughout the cerebrum, cerebellum, pons, medulla and spinal cord showed, with great uniformity, distinctive changes of a type not usually encountered in the brain of the ament. In general, these bore a striking resemblance to the appearances found in amaurotic family idiocy.

The cell bodies were swollen, pear shaped or spherical, the nucleus pushed to one side—usually towards the apical dendrite—and often shrunken or pyknotic, the nucleolus being conspicuous and the Nissl substance reduced in amount. Occupying the cytoplasm of the basal portion of the cell a granular substance formed a conspicuous mass, which in frozen sections stained readily with appropriate stains (fig. 3).

Swelling of dendrites was nowhere a conspicuous feature, though in some localities they showed an abnormal affinity for aniline dyes which enabled them to be visible some distance from the cell body; they did not appear to be noticeably fewer than normal. In cresyl violet preparations some of the larger nerve-cells showed an endocellular network replacing the Nissl substance, and Bielschowsky preparations frequently revealed a dislocation of neurofibrils to the cell periphery, this change being apparently due to the infiltrating substance. Here and there ghost-like outlines of cells in the process of disintegration could be observed, but, side by side with abnormal cells, were others in which little or no departure from the normal could be detected. The Betz cells, those of the hypoglossal nucleus, and many of the larger motor cells in the anterior horns of the spinal cords, were less affected than the medium and large pyramids of the cerebral cortex. Cellular changes of a very similar character to those found in the medium pyramidal cells also existed in the basal ganglia, but in the optic thalamus the granular deposit filling the large cells was coarser and more conspicuous than elsewhere.

A comparison of the foregoing cell changes with those found in amaurotic idiocy showed an obvious similarity, though the extreme degree of ballooning, distending a cell to perhaps three times its normal diameter, was not seen, nor was the degree of involvement of the cell processes as great as in Tay-Sachs' disease.

Though no part of the nervous system existed without the presence of altered nerve-cells containing a granular deposit the cellular reactions were more marked in some situations than in others. Thus in the cerebral cortex the deeper lying pyramids appeared more involved than those near the surface, and profoundly altered cells were particularly numerous in the optic thalamus, the mid-brain, the dentate nucleus of the cerebellum and the inferior olives of the medulla.

Staining reactions of the granular deposit in nerve-cells.—In unstained sections a very faint yellow tinge could sometimes be discerned in the cytoplasm; usually, however, the granules were colourless. In sections of cortex stained with Scharlach R the deposit acquired a pale orange red colour; in the cells of the optic thalamus the colour was a deeper red. With Nile blue a

dark blue colour was obtained; with thionin and toluidin blue a greenish yellow coloration; and with cresyl violet a dark purple. Pyronin methyl green gave a very fine differential staining of nerve-cells. The nucleus and Nissl substance stained lilac, the nucleolus dark red and the granular substance a brilliant green. For the identification of the granular substance hæmatoxylin stains proved less satisfactory, but as a rule the granules stained a brownish black. Marchi's method failed to impart any colour. The method of Loyez gave a bluish black. Gram's stain gave no differential staining. The appearances in Bielschowsky preparations varied; in some cells a reticular formation of the cytoplasm with a dark periphery of neurofibrils could be seen; in others the expanded cell bodies appeared to be occupied by fine dust-like granules.

Frozen sections mordanted for two days in bichromate solution gave the deposit in some nerve-cells a faint brownish colour, and, with four days mordanting, the colour darkened to a brownish black. Some cells remained unaffected.

In the cells of the zona compacta of the substantia nigra it was possible to identify both the normal melanin pigment and the abnormal lipoid substance which was found in all the nerve cells of the brain.

It was noteworthy that even in ganglion cells which had preserved their normal contour and size appropriate staining methods seldom failed to reveal the presence of the intracellular deposit.

Cerebellum.—Changes in the cerebellum were inconspicuous. Purkinje cells showed distortion in shape owing to the presence within them of the granular deposit, but on the whole they were well preserved and had not suffered numerical loss except in a few folia. The folia seemed finer and more delicate than normal, the molecular and granular layers being reduced in width and the cells in the latter clumped into tigroid masses. In Bielschowsky preparations normal basket fibres could be detected.

Nerve fibres.—In spite of the marked changes in the cell bodies the nerve fibres and their myelin sheaths were well preserved. In a few cortical areas the tangential fibres appeared less dense than normal; otherwise satisfactory staining was found in all areas.

Neuroglia.—In the area of the large cortical scar there was a marked excess of fibrous glia, but in nearly all other cortical regions the changes were slight. The occipital cortex was exceptional in showing a marked overgrowth of fibrous glia in its outermost lamina.

Much more striking were the changes in the basal ganglia. Beneath the ependymal surface of the caudate nucleus, in the optic thalamus, and in the hypothalamus rostral to the plane of the mammillary bodies, there was a marked gliosis; gliosis also existed beneath the ependyma of the floor of the fourth ventricle.

In several localities proliferated oligodendroglia, forming long chains, could be seen in the white matter.

In two localities—the prefrontal and precentral cortex—compound granular corpuscles were present in the subcortical white matter. Within microglial

cells the infiltrating substance was found in one or two sections only, but, in a limited number of areas, numerous masses and droplets of a peculiar lipoid-like substance were found lying free in the tissues. These are described below.

Mesodermal tissues.—No abnormality of the pia-arachnoid was found except on the area of cortical scarring where it contained numerous fibroblasts, lymphocytes and particles of yellow pigment.

Blood-vessels.—The basilar, vertebral and internal carotid arteries were healthy. Many of the smaller vessels of the lenticular and caudate nuclei and of the optic thalamus were surrounded by droplets of the lipoid substance already referred to. The staining reactions and solubilities of this deposit appeared to differ in certain particulars from any hitherto recorded. They therefore merit a full description.

Lipoid deposit.—In unstained brain tissue the actual lipoid substance was invisible to the naked eye, but its situation was revealed by polarized light, the droplets showing up as dazzling points of white light against a black background. The size of the masses varied. Very often they appeared as minute drops, about 20 to 30μ in diameter, closely aggregated round vessels and not diffusely scattered throughout the tissue. Often the fusion of separate masses gave the appearances of complete rings or masses in the adventitial spaces of vessels. Mulberry-like masses with blurred margins were also present. Evidence of inclusion of this substance within cells was scanty. Possibly a few microglial cells of the putamen contained small droplets, though on this point it was difficult to be certain as almost all the material lay free in the tissues and may have been lying on rather than within these cells. Only in one or two sections could the material be seen within the lumen of blood-vessels.

Staining reactions.—The behaviour of the lipoid substance to different stains was as follows :—

Acid dyes: It remained unstained by acid fuchsin, brilliant green, Congo red, eosin, light green, orange G, van Gieson. *Basic dyes*: cresyl violet, rose red ; methyl violet, colourless ; mucicarmine, rose red ; neutral red, orange red ; safranin, orange yellow ; thionin, lilac, red or yellow ; toluidin blue, lilac. *Natural dyes*: Hæmatoxylin, light blue. *Methods*: Bielschowsky, unstained ; Giemsa, rose red ; Holzer, unstained : iron hæmatoxylin, black ; Loyez, unstained ; Marchi, unstained ; Nile blue, unstained ; Scharlach R, unstained ; Unna-Pappenheim, unstained.

For neutral red this substance had a special affinity, the appearance in celloidin sections being that of brilliant orange red droplets. With aniline blue as a counterstain an even more effective picture was obtained, the deposit standing out with unusual distinctness against the dark blue background.

Solubilities.—Frozen sections which had been dried were immersed in different fluids at room temperature for about ten minutes, after which they were again dried and then examined in water with polarized light. The lipoid deposit behaved as follows : (*a*) cold water, insoluble ; (*b*) absolute alcohol, insoluble ; (*c*) acetone, insoluble ; (*d*) ether, insoluble ; (*e*) benzene, insoluble ;

(*f*) chloroform, partly soluble; (*g*) hot chloroform, totally soluble; (*h*) hot xylol, totally soluble; (*i*) chloroform and methyl alcohol, equal parts, totally soluble; (*j*) boiling absolute alcohol, totally soluble.

The results were perfectly clear cut: either the deposit disappeared in a few seconds or it remained totally unaffected. The only exception was with chloroform, in which the brilliantly shining mass faded rapidly to a pale white haze which did not alter with further immersion.

Melting point.—When watched on a hot stage, the masses showed clearing and loss of double refraction when the water in which they were observed was just on the point of boiling.

Distribution.—The deposit was most abundant in the globus pallidus (fig. 4) and in diminishing amounts in the putamen (fig. 5), caudate nucleus, optic thalamus, zona reticulata of the substantia nigra and dentate nucleus of the cerebellum (fig. 6). In the cerebral cortex it was found only in two localities—the pre- and post-central cortex. A small amount was also found lying in the grey matter of the cerebellar hemispheres, and in one or two situations actually free between folds of pia mater covering the folia. The substance was not found in the white matter of the cerebrum and cerebellum.

Although no difficulty was experienced in locating even minute masses with the aid of polarized light, a remarkable and puzzling feature was the fact that it could not be identified when frozen or paraffin sections were stained by any of the ordinary acid or basic dyes. Only when stained celloidin sections came to be scrutinized was it possible to identify the material. That it should not be seen on paraffin sections was to be expected since being soluble in hot chloroform and xylol it would have been removed in the process of embedding but its failure to appear in frozen sections raised the question whether the treatment incidental to the celloidin method of embedding had in some way converted a normally unstainable substance into one which readily took certain basic dyes. To this question we shall return later.

Chemical Analysis of Brain Cortex and White Matter.

Our estimations were limited to the determination of the total lipoid, cerebroside and water values.

Methods.—A block measuring about 1½ by 1 by 1 in. was removed from the medial surface of the left frontal lobe anterior to the rostrum of the corpus callosum, freed from membranes and cut into slices. From each slice grey and white matter were separated, the border line between the two being avoided. Analyses were then made using a slight modification of the procedure previously described by one of us. For purposes of control material was obtained from the brains of three psychotic subjects who during life presented no evidence of neuronic degeneration.

The results of the analyses are given in the following table.

	Per cent. cerebroside				Per cent. water	
	Cortex		White matter		Cortex	White matter
	Dry	Wet	Dry	Wet		
Patient M.	1·74	0·250	5·15	1·32	85·6	74·4
Control 1	3·09	0·505	4·89	1·48	83·7	69·8
Control 2	2·91	0·490	6·41	2·10	83·1	67·2
Control 3	2·77	0·491	5·61	1·89	82·3	66·3

Case 2.—A. W., a female child, aged 3 years, was admitted to Tooting Bec Hospital on June 13, 1918. She was one of three siblings, the offspring of healthy parents. Her younger sister who suffered from the same condition was reported in the series collected by Ellis and his co-workers. The defect was said to have been present from birth.

State on admission.—Height 30 in. Weight 26 lb. The patient was a well-nourished child with a large head, brachycephalic in conformation. Measurements of cranium (April, 1921): Circumference, 19 in.; length, 7 in.; breadth, $6\frac{1}{4}$ in.; height, $3\frac{3}{8}$ in.; cephalic index, 89. Eyebrows prominent and strongly marked, nose short, with depressed bridge and nostrils directed forwards as well as downwards. Epicanthus. Pupils normal. Angular deformity of the spine. Small umbilical hernia.

The mental state was one of idiocy, the patient being listless, unable to stand, incapable of articulation and dirty in habits. A photograph taken about this time shows a round-faced child with a heavy expressionless face, not, however, typical of the gargoyle. Three years later there was a marked alteration. The features were now peculiarly unchildlike, and unmistakably those of the type. The increased weight and general appearance of the patient had led to a diagnosis of cretinism; and thyroid treatment had been employed, but without improvement. The condition of the cornea was not mentioned. In 1924 she succumbed to congenital heart disease, aged 9 years.

Post-mortem examination: thirty-six hours after death.—The body was that of a well-nourished girl. Œdema of extremities and umbilical hernia were present. Bossing of the frontal and temporal regions was noted, and a photograph of the base of the skull taken by Dr. T. Brushfield showed a sella turcica much enlarged in all its dimensions. The dura mater was considerably thickened, the pia-arachnoid congested. The brain was large, soft, simply convoluted, and the cerebellum disproportionately small.

Weight of brain unfixed was 1077 g.; after twelve years' immersion in formalin it weighed 927 g. The right cerebral hemisphere was 408 g., the left 412 g. The cerebellum and brain-stem weighed 107 g. The lungs were congested. The heart weighed $4\frac{1}{2}$ oz.; there was mitral and tricuspid congestion and hypertrophy of the left ventricle. The liver, which weighed 567 g., was firm, congested, and relatively small. The spleen was of normal size. The

kidneys weighed 85 g. and showed fœtal lobulation. The thymus was persistent and the size of broad bean. The thyroid was large.

Microscopic examination.—Thyroid : Changes of a striking character were evident. The vesicles were of medium size, and many of them were broken down or running into each other. Some were partly filled with small masses of colloid, staining darkly with hæmatoxylin. The cells lining the alveoli were either low, cubical or flattened. The stroma was in great excess, giving a picture of marked fibrosis, and the whole appearance was that of a glandular structure which had undergone a considerable degree of parenchymatous atrophy (fig. 7).

Liver : Only paraffin embedded material was available for study, and in sections stained with hæmatoxylin and eosin there was evidence of slight degree of fatty change and of chronic venous congestion. No foam cells could be found.

Nervous system : The cerebral convolutions were of normal pattern with no evidence of wasting. There was no asymmetry and no evidence of hydrocephalus. Both pyramids were poorly developed, but the olivary bodies were unusually prominent. On the mesial surface the splenium of the corpus callosum and the pulvinar seemed unusually exposed.

The brain had unfortunately suffered by its prolonged immersion in formalin, and, when cut into slices, showed a tendency to develop countless small fissures, so that successful manipulation of frozen sections was a matter of great difficulty. Furthermore, microscopic examination of the cortex gave every indication of post-mortem artefact.

Changes quite unlike those known to occur in any pathological state were present in the ganglion cells ; they showed fragmentation and partial disappearance of the cell bodies, with contrastingly well-preserved swollen nuclei. In many situations the latter were covered with granular incrustations. In spite of these difficulties, which were chiefly confined to the cerebral cortex, it was possible to find areas relatively free from post-mortem artefact, and in these small accumulations of intracellular deposit were found within the nerve cells. Except in one or two localities this was insufficient to cause either ballooning of the cell body or displacement of the nucleus. With Scharlach R the inclusions stained a feeble yellow, but with Nile blue nerve cells containing dark blue granules were seen in every region studied. These changes were least evident in the cerebral cortex, and most marked in the groups of large cells within the optic thalamus (fig. 8) and in the cells of the inferior olivary nuclei. In the latter the changes were just as marked as in Case 1, ballooning of the cell bodies being pronounced. As in the first case, the cell processes were relatively well preserved.

The Purkinje cells showed little alteration, but the cells of the granular layer were reduced in number. In four cortical regions the cellular richness of the individual laminæ was much below the normal.

The Betz cells and the cells of the substantia nigra and hypoglossal nuclei were well preserved.

No free lipoid-like deposit could be identified with polarized light, but in view of the age of the material it was not thought worth while making a prolonged search for its presence.

As in Case 1, Holzer's stain disclosed a marked degree of gliosis in the optic thalamus and in the region of the paraventricular nucleus of the hypothalamus. In this case, too, gliosis existed beneath the ependymal lining of the floor of the fourth ventricle. In addition, gliosis was present in the region of the olives where it was not found in Case 1.

Discussion.

As far as we are aware in only one previously reported case has it been possible to record the pathological findings. This was in the first of the two patients reported by Gertrud Hurler, and the histological examination was made by Tuthill, who until his report had been completed did not apparently appreciate that the case he was dealing with was one of osseous dystrophy. The title given to his paper was "Juvenile Amaurotic Idiocy: Marked Adventitial Growth Associated with Skeletal Malformations and Tuberculomas," and, for this reason perhaps, it failed to attract the attention which its importance merited.

Summarizing the chief pathological findings in his case, it may be said that the architectonics of the cortex were undisturbed save in the region of the tubercles and in the temporal lobe near the cornu ammonis where there was a loss of cells in the third layer.

Changes in the ganglion cells involved all parts of the cortex; balloon-shaped cells, slight puffing of the dendrites and axons, and complete absence of Nissl bodies were observed. The cytoplasm had the appearance of a net-like substance owing to the presence of granules which stained a dark blue with toluidin blue, black with Weigert's myelin stain, and yellowish red with Scharlach R. Cells in all degrees of morphological change contained an infiltrating substance. The cellular changes were particularly marked in the basal ganglia and in the brain-stem, but slight elsewhere. In the white substance of the hemispheres thinning of the myelin sheaths was universal. The optic nerves showed a complete loss of myelin. The cortical glial cells were increased in size, but not in number; and near the larger vessels cells containing lipoid could be seen. Lipoid-containing cells, similar in size to oligodendroglia, were scattered sparsely throughout the white matter and a few areas contained typical fat granule cells.

In the cerebellum, brain-stem and spinal cord the vessels showed a moderate adventitial increase, but in the centrum ovale and basal ganglia the adventitia was developed to an extraordinary degree: in

some situations it appeared to be twice as wide as the vessels themselves, being composed of a fibrous network in which were many nuclei. Fine and coarse blue-staining granules were present in the adventitial spaces, around nerve and glia cells, and in masses in the meninges. Although readily stained with thionin they were scarcely visible with hæmatoxylin-eosin and not at all with van Gieson's stain. Only the nuclear aniline stains brought them into view—and only in alcohol-fixed material was it possible to stain them.

The tubercles present lay open to the meninges and were typical of tuberculous disease.

Discussing these changes, Tuthill gives it as his opinion that the enormous growth of the adventitia represented an attempt to absorb the blue staining granules which had accumulated in the perivascular spaces. The possibility that the latter—found only in alcohol-fixed material—were artefacts, is dismissed in favour of the view that they must have originated in the spinal fluid, it being pointed out by Tuthill that they were observed only in the meninges and the perivascular and perineural spaces. Such an explanation, however, is not likely to command general acceptance, though it is not suggested here that this granular substance was an artefact due to the method of fixation for, as will be seen, the lipoid-like substance found in our first case was not dissimilar in its behaviour to certain agents for fixation and embedding.

Comparison of the histological changes with those of amaurotic idiocy.—Amaurotic family idiocy is one of the few diseases of the nervous system which can be recognized with absolute certainty by an examination of the nerve-cells, and, in our first case, their morphological appearances in every area were sufficiently arresting to leave no doubt as to the correctness of Tuthill's observation that in this peculiar disease the changes in the nervous system bear a very close resemblance to those encountered in the juvenile type of Tay-Sachs' disease.

It may be recalled that in this type of amaurotic idiocy, the cell changes, as Spielmeyer (1908) and Vogt (1907) showed, never assume the striking character of those seen in the infantile form. Cytoplasmic distension of marked degree is most exceptional, and degenerative changes in the dendrites and axis cylinders are inconspicuous. Rather is there a limited degree of ballooning of the cell body with slight swelling of the cell processes. Usually there are many normal nerve-cells and the myelin sheaths are but little affected. These changes were well seen in the cases under discussion. In the cerebral cortex swollen

nerve-cells showing partial loss of Nissl substance, and distension with a granular cytoplasmic inclusion, were everywhere in evidence. The small nerve-cells and the giant Betz cells were relatively well preserved, the medium and large pyramids showing the most change. Structural changes in the basal ganglia were equally pronounced and reached their maxima in the optic thalamus where evidence of cell destruction was more pronounced than in any other region.

This intensity of the degenerative process in the cells of the optic thalamus has been noted by Hassin (1924) in both the late infantile and juvenile types of Tay-Sachs' disease; it is also a peculiarity of this nuclear mass that the deposit within the cytoplasm of the nerve-cells exists as granules larger, coarser and more intensely stained with Scharlach R than those in other regions. Other parts of the brain in our first case in which ballooning of nerve-cells was marked were the prefrontal cortex, the mid-brain, the inferior olives and the ventral horns of the spinal cord. No accentuation of the process was seen in the occipital region.

In the cerebellum few of the Purkinje cells had escaped, and in some folia they had suffered an actual reduction in number. Though no appreciable degree of atrophy was apparent to the naked eye, sections of the lateral lobe and vermis showed in the granule layer a delicacy of structure indicative of a slight degree of cerebellar atrophy. In this relative integrity of the cerebellum the histological features showed a departure from those seen in juvenile amaurotic idiocy.

The staining reactions of the intracellular substance bore a close resemblance to those encountered in Tuthill's case, and in the now well-known juvenile type of Tay-Sachs' disease. Secondary degeneration implicating the myelin sheaths was almost entirely absent, sections staining well by the methods of Loyez and Weigert.

Gitter cells were seen in two areas, but the heavy mantle of fat granules described by Tuthill as surrounding the demyelinated optic nerves was not seen, the appearance of these nerves being in every way normal. In addition to gitter cells evidence of glial reaction of a more chronic character was found. This was curiously patchy in its distribution and without any obvious relation to the degree of nerve-cell degeneration. Holzer preparations showed that this consisted of a dense interlacement of fine glial fibres and that it was most evident in the optic thalamus.

The nervous tissue from our second case was unfortunately in an unsatisfactory condition for microscopic study, but in spite of post-

mortem influences it was possible to determine the presence of the characteristic abnormal substance within the nerve-cells. The impression given, however, was of a much earlier stage in the process, only a few of the nerve-cells showing marked swellings. This is what might have been expected as the patient succumbed to valvular disease of the heart in her ninth year.

The lipoid deposit free in the tissues.—Considerable interest attaches to the finding of an anisotropic lipoid substance in the cerebral cortex, basal ganglia, mid-brain and dentate nucleus of the cerebellum. Without isolation and chemical analysis it is obviously impossible to state with confidence what the substance was, but such evidence as there is suggests that it was composed mostly of cerebrosides—phrenosin or kerasin or a mixture of both. Only in relation to its solubility in cold chloroform is there any doubt. All the known lipoids are completely soluble in chloroform, but this substance did not entirely disappear with this treatment. None the less, from our limited analysis it is possible to exclude certain substances commonly found in degenerative conditions of the nervous system; lecithin and kephalin by their melting point and by their solubility in alcohol; sphingomyelin by its solubility in benzene, cholesterol by its solubility in acetone, alcohol and ether; and lastly cholesterol esters by their property of staining with Scharlach R.

Collections of material, usually designated lipoid or pre-lipoid, have been noted by numerous observers in the late infantile and in the juvenile forms of amaurotic idiocy, but those have invariably stained with scarlet red. It is therefore obvious that there can be no likelihood of their identity with the material under discussion. In its behaviour with certain stains this substance had some points of similarity to the deposits of mucin or mucin-like bodies which have been found in the central nervous system by Grynfeltt (1923), Lhermitte (1924) and others. Like mucin, it showed a special affinity for Mayer's mucicarmine mixture, and like mucin it stained a light blue with hæmatoxylin. With neutral red and with safranine the staining qualities were also those of mucin.

A further point of resemblance lay in the influence which alcohol exerted on its stainability. It was only in celloidin sections that staining with the ordinary basic dyes took place, a peculiarity shared by mucin. According to Hiroisi and Lee (1936) though mucin will stain feebly in frozen sections, alcohol exerts a favourable influence on its staining properties, as it is found much more readily in pyroxylin

sections. Whether the grape-like areas of Buscaino (1920) are artefacts of autolytic origin, or products of mucoid degeneration, has not been finally settled; but their behaviour with stains is very like that of mucin, and under certain conditions doubly refractile crystals may be found in them. It is also significant that the blue staining granules observed by Tuthill were found only in alcohol-fixed material. Their distribution, however, was not the same as in our material. Tuthill speaks of a universal sprinkling of fine and coarse granules around ganglion and glia cells and of conglomerate masses in the meninges. The masses found in our case were limited to certain areas and were certainly not artefacts, as they could be identified in frozen sections with polarized light, nor do we think that they were in any way related to mucin bodies.

One might, perhaps, assume that being largely adventitial in distribution they represented the end-products of disintegrated nerve cells in process of removal, but for this view there is little support to be found in the histological picture, for it was never possible to find convincing evidence of this substance in neuroglial cells, and its distribution showed no close relationship to the degree of cell destruction. For example, in the optic thalamus, where cell degeneration was marked, only small amounts were present, while the largest quantities were found in the globus pallidus where cell destruction was not particularly evident. A careful study of the appearances in celloidin sections gave the impression that the deposit lay free in the tissues, and although it was certainly not an artefact, it is possible that its localization in the tissues was to some extent determined by the processes incidental to celloidin embedding. No other explanation could account for its presence in small amounts external to the pia and between folia of the cerebellum. It may be, therefore, that prolonged immersion in a mixture of alcohol and ether caused its dislodgment from one position to another.

In their description of extrapyramidal disease affecting particularly the pallidum and pars reticularis of the substantia nigra, Hallervorden and Spatz (1922) refer to deposits of pseudo-calcium in Hortega glia cells, in peri-adventitial spaces and free in the tissues. Material showing very similar properties has been described in a special form of pallido-dentate degeneration by Guillain, Bertrand and Bouques (1936). But although these substances gave a lipoid reaction, most of them could be shown to contain iron, and were therefore of a different nature to the material described above. Through the kindness of Dr. A. Meyer we have been able to examine a peculiar peri-adventitial deposit in the

pallidum of a case in which the histological features were largely those of *etât dysmyelinisé*. Just as in our case, it could be stained only after alcohol fixation, but it differed in being soluble in warm 70 per cent. alcohol and was not doubly refractile in polarized light. Fünfgeld (1929) speaks of a peculiar deposit in the lenticular nucleus of a case of status dysmyelinatus, but he gives no details of its chemical nature. It would appear then that in no previous reports has an anisotropic substance having staining reactions identical with those here recorded been described; and it is therefore unfortunate that it was not present in amounts sufficient to permit of its isolation. As already stated, on the basis of the tests for its solubility we believe we were dealing with a lipoid substance showing a close relationship to phrenosin and kerasin.

It is a peculiarity of heredo-degenerative diseases that the pathological process tends to fall specially on certain areas or systems, usually parts of the brain which are phylogenetically recent; and although it would be unwise to lay much stress on the findings in one observation it may be of some significance that the lipoid substance was most abundant in the globus pallidus, the zona reticulata of the substantia nigra and the dentate nucleus of the cerebellum—precisely those regions which are frequently involved in conditions known to be of an heredo-degenerative character.

Relation of the histochemical changes in the nerve cells to those found in the lipoidoses.—Having shown that throughout the nervous system the nerve cells exhibited morphological changes and microchemical reactions similar in every essential feature to those encountered in the juvenile form of family idiocy, it will be profitable to consider this relationship in further detail.

The recent researches of Pick and Bielschowsky (1927) have proved that, remarkable as the ballooning and distortion of the nerve cells is, these features are completely overshadowed in importance by the presence within the nerve cells of an intracellular deposit in all three types of amaurotic idiocy, and that their pathogenesis must be linked with the source of this substance. As is now well known, its presence is considered to be susceptible of only one explanation, namely, that it is the sign of a general disturbance of lipoid metabolism. Thus, amaurotic idiocy, far from being an interesting but isolated form of heredo-degeneration, is in reality only a variant of a general lipoid cellular degeneration of which there are a number of different clinical types.

Of these the most important are Gaucher's disease, Niemann-Pick's disease and Schüller-Christian's disease. With Niemann-Pick's disease amaurotic idiocy has much in common, and it has indeed been claimed that the two diseases are in reality one affection, but with different localization of lipoid storage. On the clinical side it may be recalled that in both there is a strong tendency for a racial incidence, being largely confined to Jews; that in both the condition tends to be familial; to manifest itself in early infancy and to terminate fatally before the third year of life. The evidence of a close relationship between the two diseases has also been furnished by the discovery by Goldstein and Wexler (1931) and others in subjects of Niemann-Pick's disease of the characteristic cherry red spot in the macula, an ophthalmoscopic finding hitherto regarded as pathognomonic of Tay-Sachs' disease. From the pathological standpoint the relationship is even closer. In the hepato-splenomegaly of Niemann-Pick lipoid invasion is almost universal, deposits being found not only in the reticulo-endothelial system, but also in the muscle elements, in glia and in nerve-cells. In the nervous system changes almost identical with those of Tay-Sachs' disease may be found, as Hassin has shown. Though in Niemann-Pick's disease the pathological phenomena are usually less marked, the fundamental type of change is present, the nerve-cell bodies showing the same expansion, an identical accumulation within of lipoid-like substance and microchemical changes in every way similar to those described in amaurotic idiocy. In amaurotic idiocy the visceral organs have not been studied to the same extent as the brain and possibly pathological enlargement of the liver or spleen may have been overlooked. Until recently it was believed that foam cells which are so characteristic of the lipoidoses were not present, but in a recent contribution by Brouwer (1936) reference is made to a typical case of amaurotic idiocy in which Bielschowsky was able to demonstrate their presence in the spleen, thus establishing another link between these two conditions. Not every case, however, of Niemann-Pick's disease exhibits changes in the nervous system. It would appear, therefore, that while the lipoidoses have as an underlying factor common to all a profound disturbance of metabolism, there exist differences in the type of tissue affected. When the disturbance exercises its greatest effects on the nervous system the Tay-Sachs' type is developed; when on the visceral organs Gaucher's splenomegaly appears; and when it involves the entire body the Niemann-Pick or Schüller-Christian types are the result.

Schüller-Christian's disease is characterized histologically by a diffuse

collection of lipoid cells, cellular reactions and fibrosis in various organs of the body. In the nervous system the ganglion cells are not extensively involved, nor do they show intracellular deposits. Important changes, however, are found in the white matter. According to Davison (1933), there may be found numerous demyelinated plaques, patchy in distribution and filled with compound granular corpuscles and giant glial cells. In the tuber cinereum extensive fibrosis and gliosis may occur. Foam cells occur in large numbers in the visceral organs of the body, and Chiari (1933) and Davison (1936) have succeeded in detecting their presence in small numbers in degenerated areas of the central nervous system. In Gaucher's type of hepato-splenomegaly, although it is exceptional for the nervous system to be implicated, changes do occur, especially in the juvenile form. In the case of a male infant, reported by Lindau (1930) examination of the markedly enlarged liver and spleen revealed the presence of typical Gaucher cells, while in the nervous system the ganglion cells, especially those of nucleus dentatus, showed morphological changes identical with those found in amaurotic idiocy. The intracellular lipoid inclusion was, however, microchemically inactive.

Nature of the granular deposit in the ganglion cells.—Chemical studies have proved that in this clinical group different lipoids are at fault. According to Epstein and Lorenz (1930), in Gaucher's disease the lipoids are predominantly cerebrosides, chiefly kerasin; in Niemann-Pick's disease the phosphatides are in excess; and in Schüller-Christian's disease cholesterol and its esters predominate. As regards the fourth member of this group, namely Tay-Sachs' disease, chemical analyses have not always yielded consistent results. Weston Hurst (1925), in his study of the lipoids in neuronic degeneration, came to the conclusion that in the juvenile form the abnormal deposit within the nerve cells consists of cerebrosides and phosphatides liberated from chemical combination with some other cellular substance. In a more recent publication Epstein (1931) concludes that in Tay-Sachs' disease we are dealing with a particular form of lipo-phosphatid degeneration.

In our first case the abnormal substance contained within the nerve cells was found to be almost insoluble in acetone, alcohol, chloroform and a mixture of methyl alcohol and chloroform. It was not doubly refractile, and in these properties and in its staining reactions it showed a close, if not identical, resemblance to the granular deposit described by Weston Hurst in a case of cerebromacular degeneration. Its insolubility in chloroform shows that this intracellular substance, if it

be of a lipoid nature, exists not in pure form but rather as a compound of lipoid and protein.

Chemical Analyses.

The amount of water in the brain of M.—85·6 per cent. in the cortex and 74·4 per cent. in the white matter—was within the limits of the normal, the figures approximating to those reported by Schiff and Stransky (1921) in normal man, and by Ashby and Glynn in the brain of the mental defective.

The total lipoids of the grey matter, 4·34 per cent., and of the white matter, 13·2 per cent., were below the normal, but not markedly so when comparison is made with the figures reported by Ashby and Glynn (1935). When, however, the cerebrosides are considered a very striking departure from the normal is found. Compared with the three controls the figures obtained for the cerebral cortex were very low, being in fact about one-half of the values of the three controls. In the white matter, however, there was no significant reduction in cerebrosides.

How are we to interpret these results?

It is known that cerebrosides show a definite relationship with age, their relative quantity increasing during the first two years of life as myelinization proceeds, while in the later decades the brain suffers a fall in cerebrosides, as, indeed, in all lipoid substances. The age of our patient at death precludes the age factor as a possible influence in determining the diminished cerebroside content, and his mode of dying —sudden collapse after apparent recovery from an attack of bronchitis— does not suggest that the depreciation of lipoid values in the brain could have been a terminal event secondary to some toxic influence, which is also known to influence quantitatively certain of the chemical constituents of the brain.

Of more importance is the question of whether the decrease in the percentage of cortical cerebrosides was related to the profound degree of amentia present, in the sense that chemical changes of this character may be a peculiarity of the idiot's brain. Here it may be said at once that there is no evidence in the literature available to suggest a significant correlation between the mental age of aments and their brain lipoids. A state of complete idiocy is quite compatible with a normal lipoid content in the brain. Tilney and Rosett (1931), for example, found a surprisingly high percentage of lipoids in the brains of two mental defectives, while Ashby and Glynn, utilizing for their study the brains of sixty-two mental defectives and nine normal controls, found

no appreciable change in the cerebroside content of the ament's brain. We have already suggested on clinical grounds that this type of osseous dystrophy must be considered a lipoidosis, and we consider that the results of the chemical analyses of the brain of this patient are not inconsistent with this view. As the term lipoidosis connotes, the factor common to all its forms is a disturbance of lipoid metabolism with a storage of various forms of lipoid in the organs and tissues of the body. This piling up of lipoid material may, however, be unevenly distributed, for even in one of the best-known types—Niemann Pick's disease—its distribution is by no means always constant; in some cases the excess of lipoid is confined to extraneural tissues, the brain being apparently normal, while in others there may be histological evidence of lipoid storage in the nervous system as well as in the liver and spleen. Few investigations of a chemical nature appear to have been undertaken; in regard to the brain, in one case of Niemann-Pick's disease Sobotka, Epstein and Lichtenstein (1930) reported an increase of both phosphatides and cerebrosides, and in another investigated by Klenk (1935) the sphingomyelin content was very high and the cerebrosides almost completely absent.

It may be recalled that in our first case the cerebral hemispheres contained many droplets of lipoid substance chiefly confined to the basal ganglia, and that from microchemical tests these were assumed to be composed of cerebrosides. Since they lay free in the tissues, their presence could hardly be looked upon as evidence of lipoid storage, but their obvious relationship to the perivascular spaces did suggest the presence of an abnormal substance undergoing a slow process of removal from the grey matter, and the results of chemical analyses appear to accord with this view.

Our failure to find any reduction of cerebroside in the white matter is of interest, and can perhaps be related to the absence of histological evidence of myelin sheath degeneration.

Clinical considerations.—In addition to the histological manifestations of a generalized disturbance of lipoid metabolism common to this group, it is possible to point to a number of clinical features which are shared by each type. First, it may be noted that though differing widely in their rate of progress and in their degree of menace to life, each of these five diseases, all undoubtedly of congenital origin—Gaucher's disease, Niemann Pick's disease, Schüller-Christian's disease, Tay-Sachs' disease and gargoylism — usually shows a latent period of freedom from symptoms in the early months or years of life during which the subject

presents a specious appearance of good health. This is most noticeable in the infantile form of amaurotic idiocy, in which symptoms regularly appear between the third and sixth months.

Secondly, enlargement of the liver and spleen is of great diagnostic significance. Attaining its maximum degree in Gaucher's disease, it also forms an essential part of the picture in Niemann-Pick's disease, and is usually seen in Schüller-Christian's disease and in gargoylism. Only in Tay-Sachs' disease is this enlargement of visceral organs unusual.

Thirdly, evidence of endocrine dyscrasias is not an unusual finding in at least four of the types. In Gaucher's disease (juvenile form), and Niemann-Pick's disease, infantilism has been noted; in Schüller-Christian's disease dwarfism and Fröhlich's syndrome are of frequent occurrence; in Tay-Sachs' disease Velhagen (1932) has recorded the presence of dystrophia adiposo-genitalis, while in gargoylism evidence of endocrine disturbance in the shape of dwarfism and cretinoid features is almost invariable.

And fourthly, we may note the almost constant presence of osseous lesions and deformities. According to Pick (1933) there is a form of Gaucher's disease that is clinically and anatomically preponderantly osseous, scarcely a bone being spared, but apart from this, lipoid infiltration of the bone-marrow leading to decalcification with resultant gross deformity, and sometime spontaneous fracture, is extremely common. Numerous writers in the past have recorded cases exhibiting kyphosis of the dorsal or upper lumbar spine; and more recently Bloem, Groen and Postma (1936) have called attention to the predilection of the osseous lesions for the lower end of the shaft of the femur. In Niemann-Pick's disease skeletal involvement has been described by Herzenberg (1928). In Schüller-Christian's disease the formation of lipoid deposit in bone is invariably marked by a progressive and extensive decalcification so that large portions of bone may disappear. The geographical skull—the so-called "Landkartenschädel"—which results from calvarial destruction is one of the most constant features. Again, in gargoylism the extremities of the femora and the vertebræ are almost constantly involved, and, although it is not yet proved, it is probable that these changes may be explainable on the basis of lipoid hyperplasia of the bone-marrow.

In the light of the foregoing considerations, it seems difficult to avoid the conclusion that this form of chondro-osteo-dystrophy, gargoylism, is not an isolated disease; but that it belongs to that group of diseases

of which a difficulty in metabolizing lipoids is an essential feature, and further, that it possesses in its neuro-pathological aspect a very close relationship to the juvenile form of amaurotic idiocy. There is, however, one important clinical difference. Whereas in amaurotic idiocy, once the disease has become manifest there is, as the title suggests, mental defect of an obvious and progressive type, in gargoylism the degree of intellectual retardation may vary within a wide range. It may either be so slight as to escape recognition, or, as in the former disease, be in the lowest grade, namely idiocy. Whether this variation can be correlated with the histochemical changes in the nerve cells seems more than doubtful, for in our second case, though there was little evidence of an abnormal deposit within in nerve cells, the mental grade of the patient was that of an idiot.

We share the dislike of many workers for eponymous titles, but since the other four diseases in this group have by common usage been designated by the names of those writers who have contributed largely to their elucidation, we consider that at this juncture it would be inadvisable to depart from the practice. We suggest, therefore, in place of the title "Gargoylism" the title "Hurler's disease." Under the generic term "Lipoidoses" there would thus be at least five clinical types—Gaucher's disease, Niemann-Pick's disease, Schüller-Christian's disease, Tay-Sachs' disease and Hurler's disease. To this group there will possibly have to be added Morquio's disease, a form of osteo-chondrodystrophy which, if not identical with Hurler's disease, bears many points of resemblance to it.

Further pathological considerations.—Before concluding this account, brief references must be made to one or two other features in the pathology of the condition.

In the diagnosis of gargoylism, or Hurler's disease as we prefer to call it, confusion with cretinism seems to be not uncommon, especially in cases seen in the first few years of life. The dwarfism, short neck, heavy expressionless features, obesity and umbilical hernia are common to both conditions, and that this relationship may be more than a casual one is indicated by the histological appearances of the thyroid gland in our two cases. It is true that the activities of this gland are influenced by so many different factors such as age, diet, infection and sexual activity, that the interpretation of the histological picture is by no means easy; but in our two cases in spite of the dissimilarity of the appearances, evidence of gross abnormality was outstanding. In the case of M. the gland had retained its fœtal character, and showed an

almost complete absence of colloid. In the second case colloid substance was present, but the secretory cells showed evidence of atrophy with a resultant fibrosis, and it is difficult to escape the conclusion that in both a marked degree of hypothyroidism was present.

The pituitary gland.—In view of the frequency with which enlargement of the sella turcica has been disclosed in radiographic examination of the skull in this condition, the presence of a much enlarged pituitary in our first case is of considerable interest. The enlargement affected both lobes, and microscopic examination failed to disclose any disturbances of the relative proportions of the three types of cell. It is, however, necessary to add that differential cell counts were not attempted. In the second case the gland was not available, but since a photograph of the base of the skull taken by Dr. Brushfield at the post-mortem showed a markedly enlarged sella, it is a fair inference that in this case too the pituitary was much enlarged.

There can be little doubt from these and other cases published that enlargement of the pituitary is a special feature of this disease, but whether this enlargement has any special significance cannot at present be determined. Possibly we are here dealing with a form of so-called thyropituitarism, and in this connection one may recall that in one of their cases Ellis and his co-workers noted a facial suggestion of infantile acromegaly. If, as Raab (1928) has claimed, lipoid metabolism is controlled by a pituitary-hypothalamic mechanism—and the pathological findings in Niemann-Pick's disease certainly support this view—the enlargement of the gland and the gliosis found in the grey matter bordering on the wall of the 3rd ventricle must be given a special significance.

Hydrocephalus.—Yet another cranial abnormality which occurs with some degree of frequency in this condition is hydrocephalus. In the case of M., though the cranium was not enlarged, a condition of unilateral internal hydrocephalus was disclosed; in the second case there was no ventricular distension. Unilateral hydrocephalus is uncommon, and in the majority of recorded cases degenerative changes have been present in the surrounding brain substance. These have usually been either a chronic leptomeningitis, an encephalitis, or vascular disease, and, given one of these three conditions, it is obvious that even without increased intraventricular pressure the softened brain substance may gradually yield before the cerebrospinal fluid which it imprisons, the process being rather analogous to the aneurysmal dilatation of a blood-vessel whose wall is defective. Such an explanation, though adequate for those cases in which the enlargement is limited to one part of a

ventricle, fails to afford a satisfactory explanation for the condition in which, as in this case, the whole cavity is uniformly dilated; and, where such exists, it is necessary to fall back on the assumption that lessened resistance of the wall of the hemisphere extends over a far wider area than the local cortical lesion would suggest. But, whatever may be the explanation, when viewed in the light of the clinical findings there is little doubt that the dilatation must have been of long standing for weakness of the right arm had been present from an early age.

The liver and spleen.—Another important peculiarity in this case is the absence of any evidence of the enlargement of liver and spleen, either in childhood or in the last years of his life. The liver was not, however, normal, as it showed a marked decrease in the bulk of its left lobe along with thickening of the capsule; and it is possible that these findings represented a shrinkage consecutive to a former enlargement, in which there had been lipoid storage. Through an unfortunate oversight, no pieces of either organ were retained for histological study, but in the second case the liver was of normal weight and the section which we were able to obtain from the Fountain Hospital showed no striking departure from the normal. In particular, no foam cells were present either in this or in any of the other organs studied, so that apart from the findings in the ectodermal system of a substance of probably lipoid nature these two cases provide no evidence of abnormal lipoid storage within the body. Nevertheless, when it is remembered that the taxonomic position of Tay-Sachs' disease has only recently been established by the discovery of histochemical changes in the spleen, it would be rash to assume that future studies of mesodermal tissues will not provide histological proof for the inclusion of this form of chondro-osteo-dystrophy within the group of diseases which constitute the lipoidoses.

Summary and Conclusions.

Two cases of the form of chondro-osteo-dystrophy termed gargoylism are here reported. In one of them a comprehensive study of the central nervous system was made, in the other a limited examination. Both cases were atypical in that enlargement of the liver and spleen was not detected during life nor found at autopsy. In both marked enlargement of the pituitary gland was present, and, in one, microscopic examination showed that this enlargement was due to a general cellular hyperplasia. Both thyroid glands were definitely abnormal, and the histological appearances, though dissimilar, suggested diminished secretion. No evidence of lipoid storage in the reticulo-endothelial system was found. A section of the liver of the second case showed neither

foam cells nor marked pathological changes. In both cases, in every part of the nervous system examined the ganglion cells showed a striking alteration, the cytoplasm being distended by the deposit of an abnormal substance, the Nissl granules reduced in number and crowded to one portion of the cell, the nucleus dislocated to one side, and the cell processes but little affected. These changes were much less evident in the second case. The lipoid material was extremely resistive to solvents, and was not doubly refractile. In addition to the intracellular deposit, masses of lipoid substance giving different staining reactions and different behaviour to solvents were discovered lying free in the basal ganglia and in certain other situations. The substance was believed to be composed of cerebrosides.

The myelin sheaths and axis cylinders were almost intact and fibrillary glial reaction was most marked in the optic thalamus and the paraventricular portion of the hypothalamus. The mesodermal elements were relatively little affected and lipoid storage cells were not found in them.

Chemical analysis of the brain in Case 1 showed a marked reduction of cerebrosides in the cerebral cortex but not in the white matter.

In Case 1 a unilateral hydrocephalus was present, and in both cases the cerebellum was a little small in proportion to the size of the cerebrum.

Except in a few minor details the histological findings in the nervous system were similar to those described by Tuthill in another case of this form of chondro-osteo-dystrophy; they support fully his claim that the appearances resemble in the closest degree those found in the juvenile form of amaurotic idiocy. The view is expressed that, notwithstanding the failure to find histological evidence of derangement of lipoid metabolism outside the nervous system, this condition must be accepted as a manifestation of such a pathological process and consequently belongs to the group of lipoidoses.

As eponymic designations have been accepted for the recognized principal types in this group, we would comply with common usage by suggesting the term Hurler's disease for this form of chondro-osteo-dystrophy.

We have to thank Dr. R. W. B. Ellis for giving information which led to our being able to secure the history and pathological material of our second case, and to express our indebtedness to Dr. Jacobson from whom they were obtained. Our thanks are also due to Dr. Meyer for the loan of slides containing abnormal chemical deposits and for his helpful interest in the findings.

PLATE V.

FIG. 1.

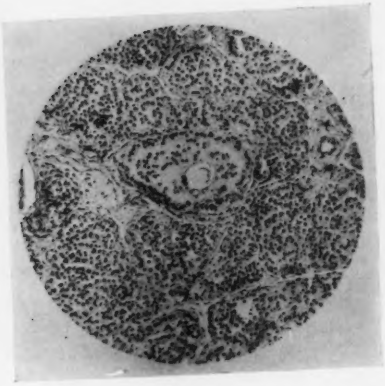
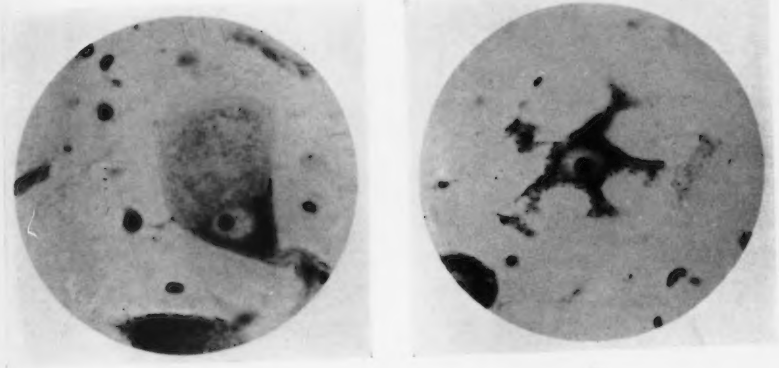


FIG. 2.



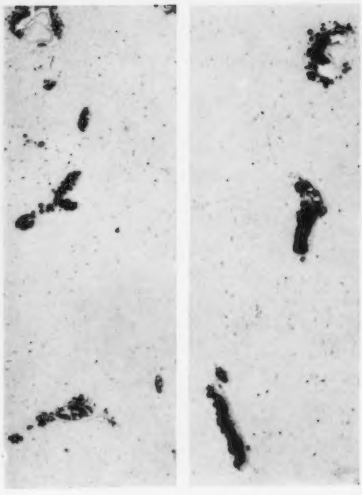
A. B.

FIG. 3.

To illustrate paper by W. R. Ashby, R. M. Stewart and J. H. Watkin.

PLATE VI.

FIG. 4.



A. B.

FIG. 5.

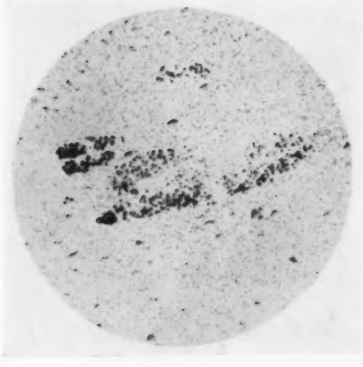


FIG. 6.

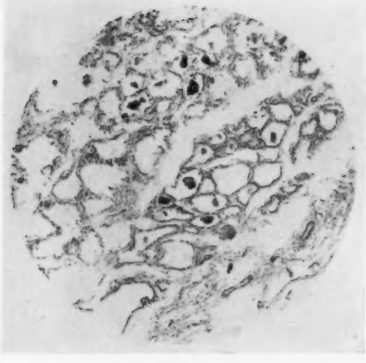


FIG. 7.

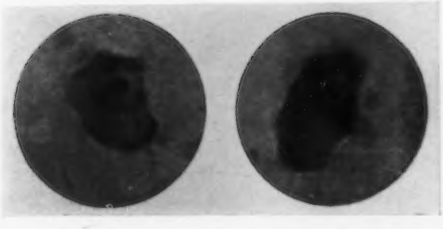


FIG. 8.

To illustrate paper by W. R. Ashby, R. M. Stewart and J. H. Watkin

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EXPLANATION OF PLATES.

PLATE V.

FIG. 1.—*Case* 1. Patient, S. M., when 8 years of age. Photograph by Dr. Brushfield.

FIG. 2.—Section of thyroid gland, for the most part consisting of solid masses of cells; one acinus near the centre of the figure contains colloid. Hæmatoxylin-eosin. × 96.

FIG. 3.—Morbid nerve cells showing various degrees of ballooning. A and B, cervical cord; anterior horn. Thionin. × 600.

PLATE VI.

FIG. 4.—Drawing showing lipoid deposit aggregated round vessels in globus pallidus. Aniline blue, orange G and neutral red. × 56.

FIG. 5.—Lipoid deposits in neighbourhood of vessels: A, putamen; B, globus pallidus. Thionin. × 25.

FIG. 6.—Small masses of lipoid in dentate nucleus of cerebellum. Thionin. × 63.

FIG. 7.—*Case* 2. Section of thyroid showing parenchymatous atrophy. Hæmatoxylin eosin. × 64.

FIG. 8.—*Case* 2. Nerve cells of optic thalamus, showing ballooning and granular inclusion. Unna-Pappenheim. × 600.

TOXIC HYDROCEPHALUS.

BY DOUGLAS McALPINE.

(From the Department of Nervous Diseases, Middlesex Hospital.)

FROM time to time cases are met with in children and young adults in which symptoms of increased intracranial pressure develop rapidly. In some of these cases the examination of the nervous system is singularly negative apart from papillœdema and an ocular palsy. The co-existence of an otitis media may clarify the position, but in other cases the cause may not be obvious and the possibility of a tumour of the posterior fossa has to be carefully considered. The purpose of the present paper is to describe a small number of cases in which an external hydrocephalus was present, and in which there was good reason to believe an infection, other than an otitis media, was the cause of the condition. Such cases have been recognized from the end of the last century under such names as "serous meningitis" and "pseudo-tumours." Quincke [6] first used the term "serous meningitis" to include a heterogeneous collection of cases, some of which appear to belong to the group which concerns us now, but at least one case was obviously an example of spontaneous subarachnoid hæmorrhage. It was not until 1912 that two papers appeared which clarified the position.

Passot [5], in a thesis, distinguished between non-purulent and purulent intracranial complications of otitis media by an examination of the cerebrospinal fluid. He described cases in which there were symptoms of increased intracranial pressure alone. The cerebrospinal fluid pressure was raised, but it contained neither an increase in the number of cells, nor in the amount of protein. He came to the conclusion that this condition was probably due to an excess of cerebrospinal fluid in the subarachnoid space, rather than in the ventricles (hydropisie méningée). Warrington [9], a few months later, in a paper entitled "Intracranial Serous Effusion of Inflammatory Origin," recorded four cases. He believed that the progress of an inflammatory effusion within the skull may be arrested at the serous stage. "The primary cause is commonly a near or distant focus of septic infection. The toxins

formed by this, but not the micro-organism, stimulate the vessels of the meninges, brain, or ependyma and choroid plexus, to the formation of excessive fluid." Symonds [8] in 1931, revived interest in this subject in a paper entitled "Otitic Hydrocephalus." He reviewed the literature of serous meningitis, referring particularly to the work of Passot, and he described three cases of his own associated with otitis media. He emphasized the main features of the clinical picture, namely advanced papillœdema in association with a general state of physical fitness, an alert mind, the absence of any localized signs, and a normal spinal fluid apart from a greatly increased pressure. The present writer shares Symonds's view on the unsuitability of the term "serous meningitis" in describing these cases. However, the adjective "otitic" adopted by Symonds to describe this type of hydrocephalus appears to have too special an implication. The term "toxic" is therefore suggested to describe the hydrocephalus which may follow, not only otitis media, but also nasopharyngeal and other sources of infection.

The following are reports of five cases in which nasopharyngeal infection seemed to be the causal factor:—

Case 1.—*Female, aged* 14. *July*, 1934, *sore throat and stiff neck followed by failing vision, diplopia, headache and papillœdema. Repeated lumbar puncture: subsidence of papillœdema and improvement in vision.*

E. L., Reg. No. 69026. Was admitted to the Neurological Ward, Middlesex Hospital, on December 15, 1934.

History.—The patient had been in normal health until July, 1934, when she developed a sore throat accompanied by a rash on the face, arms and legs. These symptoms gradually cleared up, but two weeks later they returned, and during part of this time she complained of a stiff neck, and the head was slightly drawn over to the right. Towards the end of September her mother noticed that she was holding her book close to the eyes when reading. At the end of November she had a severe "cold" in the head. This was followed by a return of the stiff neck, now accompanied by headache. On December 1 she complained of double vision on looking to the left. There was no vomiting. Mr. Maurice Whiting saw her on December 14 and noted that the vision was, right $\frac{6}{24}$, left $\frac{6}{36}$. There was bilateral papillœdema. The visual fields showed an atypical right homonymous hemianopia.

Examination.—She was admitted to the Neurological Ward on the following day. Temperature 98° F., pulse 100, respirations 20 per minute. Weight 12 st. 2 lb. The face was rounded. There was a considerable generalized increase of fat; the secondary sexual characteristics were normally developed. She complained of frontal headache. Cerebration seemed slowed, but she did not appear ill. The pupils were under the effect of atropine. There were approximately six diopters of papillœdema with exudate in both macular

regions. There was complete paresis of the left external rectus. There was no facial weakness, and no deafness, and the remaining cranial nerves were normal. Suboccipital tenderness was not found. Tone, power, reflexes and co-ordination were normal in the upper and lower limbs, and the gait was normal. The heart sounds were normal. Blood-pressure 116/60. There was no aural or nasal discharge. The fauces were injected. There was no polyuria. A lumbar puncture showed cerebrospinal fluid pressure of over 300. Cerebrospinal fluid contained 3 cells per c.mm.; protein 0·025 per cent.; Lange curve normal; Wassermann reaction negative. The headache disappeared after this lumbar puncture. She was transferred to the Hospital for Epilepsy and Paralysis, Maida Vale, for further observation.

She remained free from headache. Five lumbar punctures were performed during the next three weeks. Vision began to improve and the papillœdema slowly subsided. Diplopia disappeared at the beginning of January, 1935. The visual fields were at first generally constricted, left more than right, with a tendency, however, to flattening both above and below. Subsequently they became fuller. On January 2, 1935, Mr. T. C. Summers noted a bi-nasal defect in the lower quadrants with a 2/2000 object.

January 16, 1935: There were two diopters of papillœdema. Vision $\frac{6}{12}$ both eyes. There were signs of early post-neuritic atrophy.

February 3: The discs were now flat. The vision was $\frac{6}{9}$ (partial) both eyes.

February 7: The cerebrospinal fluid pressure was 145 mm. of water. The patient has since remained well and free from headaches. When seen on May 1, 1937, there was a moderate degree of post-neuritic atrophy. Vision was right $\frac{6}{12}$, left $\frac{6}{9}$ (partial). Menstruation was normal.

Case 2.—*Female, aged* 18. *October*, 1934, *complained of headache. One month later high-grade papillœdema without localizing signs. No definite nasopharyngeal infection. Repeated lumbar punctures were followed by disappearance of headache and slow subsidence of papillœdema. March*, 1935, *headache reappeared following a "cold"; mild papillœdema still present. March*, 1937, *discs flat, vision full.*

M. B., Reg. No. 68353. Was admitted to the Middlesex Hospital on November 27, 1934.

History.—This young married woman had been working in a factory matching wall-papers when, at the end of October, 1934, she began to suffer from dull frontal headaches. A week later, after washing her hair, she experienced severe pain at the back of the neck which radiated to the shoulders and down both arms. These pains were intermittent, but were especially noticeable in the morning and were aggravated by movement. About the middle of November she experienced pain around the eyes and nose and to a slight degree in the left ear. No history of nasal catarrh, sore throat or aural discharge could be obtained. The headache and occipital pain had subsided considerably by the time she was admitted to Hospital at the end of

November. She appeared to be a healthy young woman weighing 10 st. 2 lb.

Examination. — Temperature 98·6° F. She showed approximately 5 diopters of papillœdema each eye; a few hæmorrhages were present around the right disc; vision was $\frac{6}{6}$ in both eyes. The visual fields were full. The pupils were moderately dilated and reacted normally, ocular movements were full and there was no diplopia or nystagmus. There was no facial weakness or deafness. The remaining cranial nerves were normal. There was no abnormal posture of the head; movements of the head were free; suboccipital tenderness could not be elicited. Routine examination of the central nervous system on several occasions was completely negative, apart from depression of the upper limb reflexes. Examination in the Ear, Nose and Throat Department was completely negative, except for retracted drums and a mild pharyngitis. The heart was normal; blood-pressure was 120/75. On November 28, 1934, lumbar puncture showed a cerebrospinal fluid pressure of well over 300 mm. of water; 15 c.c. were withdrawn slowly. The headache was much relieved within a few hours. The fluid contained 2 cells per c.mm.; the total protein was 0·03 per cent.; Lange colloidal gold curve was normal, and the Wassermann reaction was negative.

Magnesium sulphate was given each day by the mouth. Lumbar puncture was repeated on December 8. The pressure was 260 mm.; 15 c.c. were withdrawn and the final pressure was 185 mm. On December 12 cerebrospinal fluid pressure was 170 mm.; 8 c.c. were withdrawn and the final pressure was 100 c.c. The patient was now entirely free from headache and the papillœdema began to subside. She remained free from headache, but 2 diopters of papillœdema were still present in March, 1935, when she contracted a severe "cold." Mr. C. P. Wilson reported that all the sinuses were clear.

She was readmitted on March 15, 1935. Lumbar puncture showed a cerebrospinal fluid pressure of 190, but on March 28 it had risen to 240 mm. and this figure was again recorded four days later. As the patient was unwilling to undergo further puncture, she was allowed to go home. On June 19 the vision was $\frac{6}{5}$ both eyes. The right fundus was normal, but there was minimal papillœdema on the left side (Mr. Affleck Greeves). On March 16, 1937, she reported herself as fit and working hard. She had continued free from headache, except when worried. Both discs were quite flat and of a good colour, but the edges of the left disc were still indistinct. Vision $\frac{6}{6}$ both eyes.

Case 3.—*Male, aged* 11. *April*, 1936, "*cold*," *frontal headache, external rectus palsy, papillœdema and impairment of vision. Rapid improvement after lumbar puncture. Antrum infected. Subsequently signs of Hodgkin's disease developed. March*, 1937, *streptococcal otitis media occurred.*

F. M., Reg. No. 92858. Admitted to Neurological Ward, Middlesex Hospital, May 13, 1936.

History.—This was obtained both from the patient, who was intelligent,

and from his father. During the first week of April, 1936, this boy complained of severe pain at the back of both eyes, and at the same time he had a "cold." The nose was "stuffed up," but there seemed to be no actual discharge. The throat was not sore, and he had no earache. The pain continued until the middle of April, when the headache disappeared, but about this time he saw double, and this persisted up to the time of his admission to Hospital on May 13.

About May 3 he had a stomach-ache, and vomited once. His father stated that after the first fortnight he had seemed quite well and had been full of fun, playing about the house. No failure of vision had been noted by the patient. There was no history of aural discharge.

Examination.—Temperature 99·8° F., pulse 108, respiration 20. The patient was mentally alert. The visual fields were full to a 1 mm. object. Vision left eye $\frac{6}{18}$, right eye $\frac{6}{12}$. About 2 diopters of papillœdema were present in each eye. There were several hæmorrhages around each disc. Both pupils reacted sluggishly to light. There was no detectable ocular paresis, but diplopia was present on looking to either side and downwards. There was no nystagmus and no facial weakness or deafness. The remaining cranial nerves were normal. There was no alteration in tone, power, reflexes, sensation, or co-ordination in the upper and lower limbs, except that the upper limb reflexes were depressed. Gait was normal. The heart was normal. Blood-pressure 118/65. There was no aural or nasal discharge; the tonsils were moderately enlarged. A small enlarged gland was felt in the left side of the neck. The liver and spleen were not enlarged and nothing abnormal was noted in the examination of the abdomen.

May 15, 1936: A lumbar puncture showed the pressure of the cerebrospinal fluid to be over 300 mm. of water; 15 c.c. were removed slowly. The final pressure was 100 mm. The cerebrospinal fluid contained 13 lymphocytes; 105 red cells; protein 0·025 per cent.; Lange curve normal; Wassermann reaction negative.

May 17: The patient no longer complained of double vision. Cerebrospinal fluid pressure was now 120 mm. of water; 3 c.c. were withdrawn.

May 18: Vision was now $\frac{6}{6}$ both eyes.

May 22: An X-ray of nasal sinuses showed slight thickening of the lining membrane of the right antrum, and to a lesser extent of the left antrum. Mr. C. P. Wilson reported as follows: "No obvious nasal discharge. Antra do not illuminate quite normally. I think there has been a definite sinusitis which is clearing up and is now practically well."

May 25: Papillœdema had further subsided. The cerebrospinal fluid pressure was 160 mm. of water. He was discharged on June 3. There was no measurable papillœdema and the vision was $\frac{6}{6}$ in both eyes.

At the end of June a painless swelling appeared above the left clavicle. He was later admitted to a sanatorium where the condition was considered to be non-tuberculous. He was readmitted to the Middlesex Hospital on

February 22, 1937. A large, firm, glandular swelling was present in the posterior triangle of the left side of the neck; a few shotty glands were felt in both inguinal regions. Several large masses were felt in the right side of the abdomen. The edge of the liver could not be felt, but the spleen was moderately enlarged. A blood-count showed a count of 13,000 white cells, of which 9 per cent. were eosinophils. A diagnosis of Hodgkin's disease was made which was confirmed by the histological appearance of a portion of the gland removed from the neck. On March 4 he developed an acute otitis media from which a hæmolytic streptococcus was grown in large numbers. There were no signs of a return of the hydrocephalus. The discs were normal and the vision was $\frac{6}{6}$. He was transferred to the care of Dr. C. E. Lakin, who confirmed the diagnosis of Hodgkin's disease, but was of the opinion that there was a secondary tubercular infection of the abdominal glands.

Case 4.—*Male, aged* 16. *July,* 1936, *during recovery from concussion, developed sore throat, severe headache, external rectus palsy and papillœdema. Ventriculogram normal. Lumbar puncture, with subsidence of papillœdema and recovery with* $\frac{6}{9}$ *vision. Tonsillectomy.*

E. W., Reg. No. 94867. Was admitted to Middlesex Hospital on July 10, 1936, under Mr. Sampson Handley.

History.—On that date he fell off a van and was unconscious for a short time. He was conscious when admitted, and there was no bleeding from the nose or ears. He was found to have a fracture of the left clavicle. No focal signs were present in the central nervous system. An X-ray of the skull was negative. He vomited twice during the first twelve hours after admission. He was lumbar punctured on July 14; the fluid was normal. During the next fortnight he complained of severe frontal headaches and he vomited on more than one occasion. During the second week in hospital he complained of double vision on looking to the right.

Examination.—I saw him for the first time on July 30. He complained of headache. He was mentally alert. Examination of the central nervous system was negative, apart from slight paresis of the right external rectus, fine lateral nystagmus and approximately two diopters of papillœdema with recent hæmorrhages around each disc. He was transferred to the Hospital for Epilepsy and Paralysis, Maida Vale, as a suspect posterior fossa tumour. During my absence on holiday, Dr. S. Nevin took charge of the case.

August 4, 1936: Vision right $\frac{6}{18}$, left $\frac{6}{9}$. Visual fields showed a generalized constriction. There was slight paresis of the right external rectus with diplopia. There was fine rapid nystagmus on looking to the right, and coarser movements to the left. Corneal reflexes were brisk, there was no sensory loss on the face. There was no facial weakness and no deafness, and the remaining cranial nerves were normal. Apart from a depression of the deep reflexes in the upper limbs, the rest of the examination of the central nervous system was negative. On August 5 he developed a catarrhal rhinitis. During the next two weeks he continued to complain of headache and vomited several times.

August 11: Cerebrospinal fluid pressure was 280 mm. of water. The fluid contained 4 cells per c.mm.; protein 0·01 per cent.; Lange curve normal; Wassermann reaction negative.

August 20: Mr. G. H. MacNab carried out a ventriculogram. The pictures were normal (fig. 1). The headaches were relieved. On September 25 he no longer complained of headaches. The papillœdema had definitely subsided and the hæmorrhages had been absorbed. Ocular movements were full and

FIG. 1.—*Case* 4. Toxic hydrocephalus. Ventriculogram. Normal anterior horns.

there was no nystagmus. A history of a sore throat during his stay in the Middlesex Hospital was obtained, and of an attack of acute nephritis one year previously. The right tonsil was much enlarged, and appeared ulcerated. A diagnosis of serous meningitis was made and tonsillectomy was advised.

September 29: Cerebrospinal fluid pressure was 230 mm. of water. 10 c.c. was withdrawn slowly, the final pressure being 120 mm. of water. The papillœdema continued to subside, so that at the beginning of October it was

not measurable. A fresh tonsillitis and rhinitis delayed the tonsillectomy until October 29.

November 10: Vision right $\frac{6}{6}$, left $\frac{6}{9}$. Cerebrospinal fluid pressure 110 mm. of water. 5 c.c. were removed. Final pressure 95 mm. of water. He was discharged to a convalescent home at the end of November apparently well. He returned to work in January, 1937. The patient has remained free from headache. When last seen on May 20, 1937, vision was $\frac{6}{9}$ both. The discs were quite flat and of good colour. An examination of the central nervous system was entirely negative.

Case 5.—*Female, aged* 11. *November,* 1936, *headache, vomiting and papillœdema, with impairment of vision and doubtful dilatation of lateral ventricles. Repeated lumbar punctures, gradual subsidence of the papillœdema and return of vision. February,* 1937, *relapse following tonsillitis. Tonsillectomy and repeated lumbar punctures. Slow subsidence of papillœdema. Normal vision.*

E. A., Reg. No. A. 1435. Admitted to the Neurological Ward, Middlesex Hospital, December 5, 1936.

History.—According to her mother the child was in good health until November 2, 1936, when she vomited, and at the same time complained of headache referred to the left frontal region and behind the eyes; it was especially marked in the mornings. These symptoms increased in severity. On November 22 she complained of a mist in front of her eyes and on the following day she saw double. About this date she appeared rather drowsy and did not want to leave her bed. From approximately November 27 the vomiting ceased and the headache diminished and had disappeared by the beginning of December. She was seen by Dr. H. L. Marriott at the Miller Hospital, Greenwich, who found papillœdema and referred her to me. No history of aural or nasal discharge, tonsillitis, boils, or any focus of infection prior to the onset of the illness could be elicited.

Examination.—On admission to the Middlesex Hospital on December 5, 1936, temperature 98° F., pulse 76, respirations 20. She was a well-nourished child with a rounded face and a slight general increase of subcutaneous fat. She did not appear ill and was not suffering from headache. She was mentally very alert and quick in carrying out various tests during the examination. Ophthalmoscopic examination showed approximately four diopters of swelling of both discs. There were two small hæmorrhages below the right disc. The vision was $\frac{6}{18}$ (partial) both eyes. The visual fields were full to a 2 mm. white object. There was slight convergent strabismus of the left eye, due to weakness of the left external rectus. The pupils were dilated and reacted somewhat sluggishly to light. Slow nystagmus was present on looking to the right. Sensation on the face was normal, as were the facial movements. Hearing was not diminished and there was no discharge from the ears. The remaining cranial nerves were normal. There was no abnormal posture of the head, and suboccipital tenderness was not elicited. The arms showed a slight degree

of hypotonia. Power appeared normal, and there were no signs of disturbance of cerebellar function. The arm reflexes were obtained with difficulty. The abdominal reflexes were brisk and equal. The lower limb reflexes were brisk and the plantar responses flexor. The gait was normal.

The apparent well-being of this child, the absence of headache, despite well-marked papillœdema, suggested that the condition might be one of toxic hydrocephalus, rather than posterior fossa tumour. It was considered necessary to tap the ventricles before carrying out lumbar puncture, in order to establish whether the hydrocephalus was of the internal or external variety. This was done by Mr. P. B. Ascroft on December 12, 1936. He found the ventricles to be slightly dilated, but the pressure was not much raised. 20 c.c. of cerebrospinal fluid were withdrawn. Attempts to inject air were unsuccessful.

December 16, 1936: The patient did not complain of headache. Cerebrospinal fluid pressure was not estimated, but did not appear much increased. 8 c.c. of fluid were withdrawn. It contained 2 cells per c.mm.; protein 0·03 per cent.; Wassermann reaction was negative.

December 20: The papillœdema appeared to be definitely subsiding and now measured approximately two diopters. There was no nystagmus. The cerebrospinal fluid pressure was 190 mm. of water. 8 c.c. were withdrawn, the final pressure being 110 mm. of water.

December 29: The cerebrospinal fluid pressure was 140 mm. of water. This lumbar puncture was followed by headache and vomiting during the next few days.

January 4, 1937: Slight headache was still present. Papillœdema now measured one diopter on the right and less than this on the left. Vision, right $\frac{6}{6}$, left $\frac{6}{9}$. There was now no nystagmus and double vision could no longer be elicited.

January 12: Both optic discs were now quite flat and the patient was free from symptoms. Re-examination of the central nervous system was negative. In view of enlarged and unhealthy tonsils it was decided to have tonsillectomy performed at an early date. She was discharged and asked to attend weekly.

January 26: She appeared perfectly well. The vision was now $\frac{6}{6}$ both eyes, and the discs were quite flat and well coloured.

February 9: Her mother stated that a week previously she had had a "cold" in the head and sore throat, and at the same time complained of frontal headache. Both discs now showed approximately one diopter of papillœdema with marked fullness of the veins. The right vision was $\frac{6}{6}$, the left $\frac{6}{9}$ (partial). There was no nystagmus and no diplopia. The fauces and tonsils were reddened and congested. The rest of the examination was negative. She was readmitted the same day. Temperature 98·4°F., pulse 80, respirations 20.

February 10: The cerebrospinal fluid pressure was over 300 mm. of water. 30 c.c. were withdrawn and the final pressure was 150 mm. of water. A Dick test was strongly positive. A swab from the throat was negative for hæmolytic streptococci.

February 12: The cerebrospinal fluid pressure was well over 300. 37 c.c. were withdrawn and the final pressure was 150 mm. of water.

February 17: Three diopters of papillœdema were now present. Vision, right $\frac{6}{6}$, left $\frac{6}{9}$. It was thought advisable to have a tonsillectomy done at once and this was carried out on this date. Just before operation cerebrospinal fluid pressure still over 300 mm. of water; 35 c.c. were withdrawn. Final pressure was 145 mm. of water.

February 19: Cerebrospinal fluid pressure was 240 mm. of water. 10 c.c. were removed and the final pressure was 140 mm. of water. The patient remained free from headache.

February 22: Papillœdema was slightly less marked and re-examination of the central nervous system was negative. The cerebrospinal fluid pressure remained over 300 mm. of water; 27 c.c. were removed. The final pressure being 145 mm. of water.

February 23: Slight headache was complained of and in view of this it was decided to discontinue lumbar puncture for the present.

February 26: "Papillœdema has considerably subsided; approximately 1·5 diopters in each eye" (Mr. R. Affleck Greeves). The patient appeared well.

March 5: Cerebrospinal fluid pressure was 220 mm. of water; 15 c.c. were withdrawn. The final pressure was 110 mm. of water.

She was discharged from hospital on April 27. When seen again on May 18 she was free from headache and appeared well. "Right disc edge still slightly blurred, but swelling not measurable. Left disc practically normal" (Mr. R. Affleck Greeves). Vision was $\frac{6}{6}$ both eyes.

Clinical Features.

Age of incidence.—The ages of the five patients reported in this paper ranged between 11 and 18 years. This age incidence agrees with the findings of Symonds that the condition is rarely met with apart from childhood and adolescence. The reason for this must remain at the present time problematical, but presumably it may depend on a greater sensitivity of the choroid plexus to the effect of toxins in the young as compared with adults.

Precipitating factors.—In none of the cases was there a history of otitis media, nor was any evidence of this condition found when the patients came under observation. In Case 2 pain was felt in the left ear during the acute phase, but the ear-drum appeared normal three weeks later. In two cases a "sore-throat," and in another two a "cold," preceded the onset of headache. An exacerbation of the hydrocephalic symptoms following a fresh "cold" occurred in three cases, being particularly clear in Case 5. In this case papillœdema and headache disappeared, only to reappear five weeks later coincidently

with the onset of a fresh nasopharyngeal infection. In this case careful inquiry failed to establish any obvious cause for the initial condition, but in view of the occurrence of a "cold" preceding the relapse, it seems reasonable to assume a similar sequence of events on the first occasion, a "cold," or a slight attack of tonsillitis, having possibly occurred at an earlier date. In Case 3 there was clinical evidence of nasal sinus infection during the acute phase, and when the child was admitted to hospital there were signs of subsiding infection of the antrum. Nine months later this patient developed a left otitis media without any return of hydrocephalic symptoms. In the remaining four cases there was no evidence of infection of the sinuses. Radiological examination at a later date in Cases 1 and 3 showed no abnormality. In Cases 2 and 5 there was "slight thickening of the lining membrane of both antra" (Dr. H. Graham Hodgson). A puncture of the right antrum in Case 5 was, however, negative.

With the exception of Case 1 the remainder had never undergone tonsillectomy, and of these four showed evidence of well-marked tonsillar infection.

In three cases in which there was a definite history of a "cold" or "sore-throat" there was an interval of one day to two weeks before the symptoms of hydrocephalus showed themselves. It is probable that although in this series of cases the latent interval appears to have been short, in some cases a longer period may elapse. A possible explanation of this might be that an attack of tonsillitis or nasal catarrh caused the patient to become hypersensitive, and that at a later date a minor recurrence was sufficient to produce a condition of allergy with its main effect on the choroid plexus.

These facts suggest that nasopharyngeal catarrh and tonsillitis have a causal relationship to certain cases of toxic hydrocephalus.

Symptomatology.—The picture of raised intracranial pressure develops quickly in the course of a few days, and reaches its maximum after a period varying from one to two weeks. There is then a tendency to improvement with the exception of ocular symptoms, the patients often feeling and appearing in their usual health. This period of what may be called compensation, may be prolonged for some weeks or months. If untreated the papillœdema may persist, or may slowly subside leaving behind varying degrees of optic atrophy with consequent impairment of vision and even blindness. In other cases relapses may occur, usually associated with a fresh infection.

The symptomatology will now be considered in more detail.

Headache is a constant feature, and is the earliest sign of hydrocephalus. In three of the cases the headache was frontal, and in Case 5 it was more severe on the left side. In Case 1 pain at the back of the neck preceded generalized headache, and the head was drawn over to the right. This was the only case in which a history of an abnormal posture of the head was obtained. Case 2 suffered from pain referred to both the frontal and occipital regions. The headache in every case was severe at the onset, and had the usual characteristics of headache associated with increased intracranial pressure. In Cases 3 and 5, the headache disappeared in three and five weeks respectively, and was still absent when they first came under observation. In the remaining three cases the headache decreased in intensity after the first week or two, but reappeared in Cases 1 and 5 with the occurrence of a relapse.

Vomiting.—This occurred only in the three youngest patients. It was a marked feature in Cases 4 and 5, and in the latter case was typically projectile in character. In no case did the vomiting precede the headache. Drowsiness was present in one case only.

Constitutional symptoms.—The three eldest patients, aged 14, 16 and 18 respectively, suffered little or no constitutional disturbance, but were inconvenienced by the headache. In the two younger cases vomiting was found distressing, and both these patients, as a consequence, felt ill. No records of temperature during the first few days were obtainable. Only one patient had a raised temperature for the first twenty-four hours under observation. An important feature of all the cases when first seen was their appearance of well-being.

Ocular symptoms—Papillœdema was present in each case. The swelling varied from 2 to 6 diopters. Case 1 showed the greatest degree; this case was seen for the first time five months after the onset. Impairment of vision was noticed by two of the patients, Cases 1 and 5, in the former approximately six weeks, and in the latter case three weeks, after the appearance of headache. Vision was found to be impaired in four out of the five cases when they first came under observation. As one would expect, the reduction was roughly proportionate to the duration of the symptoms. Case 1 illustrates this point. The right vision was $\frac{6}{24}$ and left $\frac{6}{36}$, when she was first seen five months from the onset. The earliest occurrence of failure of vision was three weeks from the onset, in Case 3, vision being right $\frac{6}{18}$, left $\frac{6}{12}$. The impression was gained that in toxic hydrocephalus, owing to the rapidity with which increased intracranial pressure develops, vision is affected earlier and to a greater degree than is usual in papillœdema due

to cerebral tumours. The improvement of vision that occurs with subsidence of the papillœdema may be quite rapid.

The *visual fields* showed no distinctive alteration beyond a tendency to generalized constriction. In Case 1 the fields were variable. Initially an atypical right homonymous hemianopic defect was found, but one week later there was a flattening of both fields from above and below. In Case 2, in which vision remained unimpaired throughout, the fields were normal. *Double vision* was complained of by four out of the five patients, and in each case it was due to a paresis of an external rectus muscle; it quickly disappeared after the first few lumbar punctures. *Nystagmus* was present in two cases; in one it was rapid and fine, in the other slow to one side. In two other cases nystagmoid movements were observed.

Remaining cranial nerves.—The 5th cranial nerve was intact. No facial weakness or deafness was observed in any case. The other cranial nerves were normal.

Posture of head.—No abnormality in the position of the head was noticed in any case that could not be accounted for by the diplopia. In Case 1 there was a history of the head being turned to the right soon after the onset. In no case was there any rigidity of the neck or impairment of movement of the head. Suboccipital tenderness was looked for carefully, but could not be elicited in a single case.

Limbs.—In the three youngest patients tone was slightly diminished in the upper limbs, but this was no greater than is usually found in children. No impairment of power in the limbs was found. Each case was carefully scrutinized for evidence for a cerebellar defect, and the usual tests were applied with completely negative results in every case. The gait in two of the patients was hesitant, and this was attributed to the double vision. With regard to the reflexes, a characteristic finding, which was present in four out of the cases, was depression of the upper limb reflexes, whilst those of the lower limbs were normally active. This is a common finding in tumours of the posterior fossa, and usually is attributed to the effects of increased intracranial pressure on the lower cervical roots. In no case was there any change in the reflexes suggesting involvement of the pyramidal tract.

Cerebrospinal fluid.—Symonds has emphasized the characteristic features of the fluid, namely an increased pressure and normal cell and protein constituents. These features were found in each of the cases in the present series. In four of the five cases the pressure exceeded 300 c.c. of water as measured with Greenfield's manometer. In Case 4

the maximum pressure recorded was 280 mm. of water. In Case 3 one specimen of the cerebrospinal fluid contained 13 lymphocytes and 105 red cells. In the remaining cases there was no increase in the number of cells, or in the percentage of protein. In every case the Wassermann reaction was negative. The number of lumbar punctures necessary in each case varied from three in Case 3, to ten in Case 5, but in this last case, as well as in Case 2, in which six were carried out, there was a relapse. The greatest amount of cerebrospinal fluid drawn off at one time was 37 c.c. The effect of the first lumbar puncture was always to relieve headache if this was present. As a rule the cerebrospinal fluid pressure subsided *pari passu* with the lessening of the papillœdema. As judged by the cerebrospinal fluid pressure, the hydrocephalus may subside rapidly. In Case 3, for example, the first puncture showed a pressure of over 300 mm., but two days later the pressure was 120 mm. and a further puncture eight days later showed the pressure to be still normal. The papillœdema in this case rapidly subsided. In Case 2 the papillœdema had not quite subsided on the patient's discharge from hospital, although the cerebrospinal fluid pressure was normal, and was still present four months after the onset. The patient then suffered a relapse following a "cold" and on readmission a pressure of 240 was recorded on two separate occasions. The papillœdema, however, had not increased.

In the remaining cases the cerebrospinal fluid pressure was normal when they left hospital. In Case 5 the papillœdema had subsided and the cerebrospinal fluid pressure was normal before discharge. Five weeks later, following a "cold," cerebrospinal fluid pressure was once more raised to over 300 mm. with an increase in papillœdema. This case illustrates well the rapidity with which the hydrocephalus may develop; namely, in the course of a few days.

The flow of fluid was always free, and this is an important point in the distinction between this group of cases and those with an arachnoiditis of the posterior fossa.

Treatment.—Lumbar puncture, as originally advised by Quincke in the treatment of serous meningitis, is the method of choice. In the first three cases this procedure and the use of hypertonic saline were the sole methods of treatment. On theoretical grounds, lumbar puncture would appear to be dangerous in the presence of a high-grade papillœdema, but in these cases, provided care is exercised, no ill-effect has been observed. In Case 4, in which the diagnosis was obscured by a head injury, a ventriculogram was carried out. This was followed by

lumbar punctures. In Case 5 the diagnosis was also in doubt, and the same procedure was followed. In these doubtful cases, once the diagnosis of an external hydrocephalus has been established, lumbar puncture can be carried out with impunity. Certain precautions should be observed during drainage by the lumbar sac. Measurement of the pressure is essential on each occasion. If, as is usually the case at the onset, the pressure exceeds 300 mm. of water, then enough fluid should be withdrawn to lower it to approximately half of the initial figure, e.g. 150 mm. of water. The time occupied by the drainage should be at least half an hour. The rate of flow can easily be controlled by half turning the cock on the shaft of the needle. Headache appearing during the drainage should be a signal that the fluid is being withdrawn too quickly, and the flow should be discontinued for a quarter of an hour and resumed more slowly. With regard to the frequency of lumbar punctures, this varies from case to case. When the cerebrospinal fluid pressure remains high, the procedure must be repeated at least every third day until the pressure begins to fall; the interval between the punctures may then be lengthened. It is desirable to obtain a normal reading before discontinuing the treatment, but this may not always be possible. The vision should be recorded at least twice a week, so as to observe the effect of treatment. If the cerebrospinal fluid pressure continues to remain high and papillœdema persists, despite treatment of the "focus" and adequate lumbar drainage, then ventricular tapping should be resorted to to make certain that an internal hydrocephalus is not developing. If this be absent, a further two or three lumbar punctures should be carried out. As long as the papillœdema remains low-grade and vision is not impaired, a waiting policy may be adopted for some months. During this time the patient must be seen every two weeks, the fundi examined and the vision recorded. If at the end of this period the cerebrospinal fluid pressure still remains much raised and vision is failing, then a subtemporal decompression should be resorted to, or if there is any evidence of a developing obstruction, a cerebellar decompression, in the hope of removing any adhesions that may be present in the region of the roof of the fourth ventricle.

Treatment of the infective focus.—It is important that any focus of infection should be treated promptly. If there be an aural discharge, then mastoidectomy should be carried out without delay. Nasal sinus infection should be dealt with, either conservatively, or by puncture, according to the type of case. In the group of cases described in this paper, in four of them it is probable that tonsillar infection played an

important part. I believe that in such cases enlarged and unhealthy tonsils should be removed as soon as the more urgent symptoms have subsided.

Results of treatment.—In the series of fifteen cases of serous meningitis reported by Davidoff and Dyke [3], thirteen were treated by subtemporal decompression, and one case had a suboccipital decompression. The symptoms cleared up and there was improvement or arrest of the failing vision. After leaving hospital they were followed for periods varying from a few months to several years. Dehydration methods were continued at home. Final disappearance of the papilloedema required from six months to several years. There was occasional return of headaches. The results in my small series of five cases treated by spinal drainage are as follows: Each of them have definitely recovered from the hydrocephalus, headache and papilloedema being no longer present. The vision is full in three cases. In Case 1, which did not come under observation until five months after the onset, there is a mild degree of post-neuritic atrophy, and vision two and a half years later is now, right $\frac{6}{12}$, left $\frac{6}{9}$, with an associated moderate degree of post-neuritic atrophy. Two years have passed since Case 2 was first seen and the vision remains full. In Cases 3 and 4, twelve months and six months respectively have elapsed. Since their discharge from hospital Case 3 subsequently developed signs of Hodgkin's disease and more recently a streptococcal otitis media which cleared up without any return of hydrocephalic symptoms, vision remains normal; Case 4 is well and at work, vision being $\frac{6}{9}$ both eyes; in Case 5, the papilloedema disappeared rapidly, only to reappear again one month later. It has subsided much more slowly but is now no longer measurable three months after the relapse. Vision up to the present remains normal.

In these last three cases final pronouncement on the diagnosis and results of treatment must wait another year or two. However, the results up to the present have been favourable, not only from the point of view of the relief of the hydrocephalus, but also of the preservation of vision. They would suggest that if the diagnosis of a toxic hydrocephalus can be established, then lumbar puncture is a safe and efficient method of treatment. In those cases where there is a doubt as to the diagnosis, then ventricular estimation should be carried out, and if this confirms the absence of an internal hydrocephalus, then no further operative interference should be necessary.

Finally, it must be emphasized that careful watch should be kept on these cases for some months after their discharge from hospital.

Only in this way will it be possible to detect relapses and ensure the correctness of the original diagnosis.

Differential Diagnosis.

The rapid development of a hydrocephalus in a young person may lead to considerable diagnostic difficulties. There are three conditions with which toxic hydrocephalus may be confused: (1) An abscess; (2) a tumour of the posterior fossa; (3) an arachnoiditis of the posterior fossa. With regard to an abscess, this is likely to prove a matter of difficulty only when an otitis media is present. Symonds has dealt fully with this aspect of the subject in his paper on "Otitic Hydrocephalus." Arachnoiditis of the posterior fossa, although a less common condition than a tumour, will be considered first. Howell [4] emphasizes that the clinical picture will depend on three factors: (*a*) The area involved; (*b*) whether or not an encysted collection of fluid has formed; (*c*) whether hydrocephalic dilatation of the ventricles has resulted from blocking of channels through which the cerebrospinal fluid circulates. In France Claude [2] and others have studied the various clinical problems arising from these three different factors. Claude stresses the importance of the following signs due to a localized collection of fluid in the posterior fossa: (1) Occipital headache aggravated by movement, effort or vomiting; (2) stiffness of the neck; (3) giddiness and unsteadiness in walking; (4) papillœdema which, however, is not constant; (5) preservation of hearing until a late stage. It would appear that stiffness of the neck, on which Claude lays stress, should be the most helpful sign in differentiating this condition from toxic hydrocephalus. In Case 1 it was probably present in the initial stage, as there was occipital pain and the head was turned to one side. This sign was, however, absent in the remaining cases when they came under observation, and there was no history suggesting that it had ever been present.

When there is a generalized arachnoiditis of the posterior fossa, the signs are more diffuse. According to Barré [1], multiple cranial nerve involvement, usually bilateral, is characteristic; there may be an irritative phase at first, followed by paresis. Cerebellar and pyramidal signs are slight, or may be absent. To this local picture are added signs of an internal hydrocephalus.

When symptoms of focal disturbance in the posterior fossa arise with or without signs of a hydrocephalus, the condition is more likely to be confused with a tumour than with a toxic hydrocephalus. There is, however, one type of arachnoiditis of the posterior fossa which may be

impossible to distinguish from an external hydrocephalus without the aid of ventriculography, namely, that form in which adhesions affect chiefly the region of the roof of the fourth ventricle, causing an obstructive hydrocephalus. The following is an example of this condition :—

Case 6.—*Female, aged* 9. *December*, 1936, *headache, vomiting, double vision and impaired eyesight. One month later, no headache, high-grade papillœdema, reduced vision, external rectus palsy, no localizing signs. Ventriculograms revealed bilateral internal hydrocephalus. Suboccipital exploration. Arachnoiditis. Secondary infection. Death.*

B. L., Reg. No. A.3398. Referred to the writer by Dr. Alan Moncrieff on January 28, 1937. Admitted Neurological Ward, Middlesex Hospital, on the same day.

History.—According to her mother this child was in good health until December 22, 1936, when she complained of headache over the left eye. The headache was intermittently present until December 27. On that day she vomited and appeared tired and drowsy. On the following few days the headache and vomiting continued and the child did not seem so well. She was seen by a doctor on December 31. He ordered her to bed where she remained until January 3, 1937. By this date the vomiting had stopped and the headache was less severe, but she complained of pains at the back of the neck and across the shoulders. On getting out of bed she appeared unsteady, and on the following day she complained of some failure of vision of the left eye, and also saw double. On January 6 she received some medicine which caused the headache to disappear, and it only recurred once or twice prior to her admission to hospital on January 28. She had not been subject to "colds" until 1936, when one occurred in the spring and the other at the beginning of October. There was no history of discharge from the ears. Early in December, 1936, she fell and hurt her head, but this did not seem to affect her.

Past history.—She had whooping-cough at the age of $2\frac{1}{2}$ years. She had never undergone tonsillectomy.

Examination.—On admission on January 28, 1937, temperature 98·2° F., pulse 96, respirations 24. She did not complain of headache. She was a bright, intelligent child, and she did not seem at all ill. There was approximately 5 diopters of papillœdema in either eye, with a few small recent hæmorrhages around the right disc. The visual fields were generally constricted. Vision in the right eye was $\frac{6}{18}$ partial, and in the left eye $\frac{6}{36}$. The pupils were dilated and both reacted sluggishly to light. Fine lateral nystagmus was present to either side. Intermittent paresis of the left external rectus was noted. Hearing was slightly diminished in the left ear, but wax was present; no discharge from the ear was seen. The remaining cranial nerves were normal. The posture of the head was normal, and there was no suboccipital tenderness. Tone was slightly diminished in both upper limbs. Power was good on both sides. Co-ordination was normal, and

she showed no tremor or ataxia. The reflexes in the arms were markedly depressed. There was no sensory loss. Abdominal reflexes were brisk and equal on the two sides. In the lower limbs power was good, the deep reflexes were active, the right knee-jerk more so than the left, and the plantar responses were flexor. She walked with undue care, but there was no swaying, and she was able to stand on either leg unsupported. There was no nasal discharge; the tonsils were enlarged and appeared unhealthy. Other systems appeared normal.

FIG. 2.—*Case* 6. Arachnoiditis of posterior fossa. Ventriculogram. Marked degree of internal hydrocephalus.

The absence of headache and the well-being of the child suggested a toxic hydrocephalus, rather than a tumour of the posterior fossa, although there was no recent history of nasal catarrh or a tonsillitis. In view of the high-grade papilloedema it was decided to perform a bilateral ventricular tap with ventricular estimation, and if there was evidence of dilatation of the lateral ventricles then air should be injected. This procedure was carried out by

Mr. P. B. Ascroft on February 1, 1937. The pressure in the ventricles was found to be very high, e.g. 490 mm. of water. Approximately 90 c.c. of fluid were removed, and air was injected. The X-ray picture showed a well-marked bilateral internal hydrocephalus (fig. 2). The 3rd ventricle did not show up well and the 4th ventricle not at all. Air was released from the ventricles two hours later.

It was now clear that we were not dealing with an ordinary case of toxic hydrocephalus, but presumably with an obstructive lesion of the iter, or of the 4th ventricle, due either to arachnoiditis of the posterior fossa, or to a mid-line tumour. The abrupt onset of symptoms of increased intracranial pressure, followed by subsidence, and the absence of any focal signs, made the diagnosis of a tumour less likely than that of an arachnoiditis. On February 2, 1937, Mr. Ascroft performed a cerebellar decompression. Repeated ventricular tapping was necessary during the first part of the operation, owing to the high pressure. The dilated 4th ventricle was opened, resulting in a great gush of cerebrospinal fluid. Adhesions were found and divided. From their position in relation to the foramina, it was certain that they were blocking the roof of the 4th ventricle. Unfortunately, the child persisted in scratching the region of the burr holes, a streptococcal infection developed which spread to the ventricles, and despite the use of Prontosil, death from meningitis resulted eight days after the operation. A post-mortem was refused.

If the history of this case and that of Case 5 be compared, the striking similarity between them is apparent.

Theoretically, at least, lumbar puncture and the application of Queckenstedt's test, with information gained as to the rate of flow and the amount of cerebrospinal fluid obtained, should enable a diagnosis to be made between an obstructive and an external hydrocephalus. Such a step, however, may be dangerous should the hydrocephalus be of the non-communicating type, and therefore it is much safer to carry out bilateral ventricular tap with estimation of the pressure and amount of fluid in the lateral ventricle, followed, if necessary, by ventriculography. The injection of a colouring matter into the ventricle, followed later by lumbar puncture, can be done if there is doubt about the size of the ventricles, or if ventriculography is, for any reason, impracticable.

Tumours of the posterior fossa.—The differentiation of a toxic hydrocephalus, in the absence of an obvious focus of infection, from a tumour of the posterior fossa, more especially of the cerebellum or 4th ventricle, may be impossible on purely clinical grounds. However, careful attention to certain details in the history may be helpful in those cases where physical signs are scarce. As a rule, the clinical picture of a tumour in this situation is characterized by slow progression. Headache, for example, due to a cerebellar tumour may at first be

intermittent, increasing in severity as the weeks pass, contrasting with the initial severe headache of a toxic hydrocephalus, which diminishes or even disappears after the first two to three weeks. Again, double vision, when it occurs in a toxic hydrocephalus, does so within the first three weeks as a rule, whereas its appearance in a cerebellar tumour is usually later. In the case of a cerebellar tumour, repeated examination will usually reveal some evidence of inco-ordination in the limbs or in walking, which is lacking in a toxic hydrocephalus.

More rarely tumours of the 4th ventricle, or of the vermis, may have an onset which is quite abrupt. Occipital pain radiating down the neck and sometimes into the shoulders, with exacerbations, is characteristic. The neck is usually held stiffly, and the head may be turned to one side or bent slightly forward. Suboccipital tenderness is almost constant. Sudden movements of the head may precipitate bulbar symptoms such as giddiness, vomiting, disturbances of respiration and of pulse, and even syncope. Cerebellar signs are usually found, but are often discrete. They consist of nystagmus, hypotonia and lack of co-ordination, particularly in walking. With the exception of occipital headache and fine nystagmus, none of the above signs are met with in toxic hydrocephalus. However, it may be impossible to distinguish between the two conditions without the aid of ventriculography.

Discussion.

Toxic hydrocephalus is a condition that occurs chiefly in childhood and early adult life. Although its association with otitis media is best known, it is probable that other sources of sepsis, such as sinusitis and tonsillitis, are equally important. More rarely, it may follow one of the infectious fevers. The cases reported in this paper illustrate the part played by nasopharyngeal infection in its causation; the rapid return of symptoms of hydrocephalus that followed a fresh "cold" was a striking feature in more than one case. Unfortunately, no systematized bacteriological investigation of these cases was undertaken. Sheldon [7] has reported a case in which there can be little doubt that a hypersensitivity to a streptococcus was the cause of the hydrocephalus. A woman, aged 23, had an attack of tonsillitis from which she had often previously suffered. Eight days later a scarlatiniform rash appeared, followed by a painful effusion into the joints, and a serous meningitis with four diopters of papillœdema. Both these conditions subsided as a peritoneal abscess due to a hæmolytic streptococcus developed, its drainage being followed by complete recovery. Sheldon comments

on the rarity of the association of effusion into the joints and a serous meningitis. He refers to a number of cases dealing with the association of serous meningitis and serum sickness. He considered that in his own case a streptococcal toxin acted directly on the synovial membranes and choroid plexuses, and he draws an analogy between a serous hydrocephalus resulting from an allergic state such as serum sickness, and a similar allergic condition in his own case. His conclusions are of interest in considering the group of cases described in the present paper. Case 1 showed the association of a scarlatiniform rash and a hydrocephalus. Three of the remaining cases indicated clearly the close relationship that exists between nasopharyngeal infection and the onset of the symptoms of increased intracranial pressure. It is of interest to note that Case 4 suffered a year previously from acute nephritis, possibly secondary to a chronic tonsillar infection; Case 3 developed an otitis media nine months after the subsidence of the hydrocephalus, unassociated with a return of symptoms; a pure culture of a hæmolytic streptococci was obtained from the aural discharge. This aspect of the problem requires further study in order to determine whether the same organism, for example a streptococcus, is pathogenic in all these cases, including the group of otitis media.

We know little or nothing of the pathological changes in the brain in this condition. The fact that complete recovery from the hydrocephalus usually takes place leads to the presumption that no permanent changes in the pia-arachnoid occur. However, it seems probable that the clinical distinction between toxic hydrocephalus and arachnoiditis is greater than the pathological one. Infection of the ear, nose and throat plays an equal part in the causation of both these conditions. In arachnoiditis adhesions occur, sometimes associated with an underlying encephalitis or ependymitis, according to certain writers. In toxic hydrocephalus, on the other hand, we suppose that the condition is merely due to a functional disturbance of the choroid plexus. It seems plausible to assume that there are cases which bridge the gap between these two conditions. For example, in the subacute type of toxic hydrocephalus, in which, despite adequate drainage, the papillœdema subsides very slowly and relapses are common, a mild degree of arachnoiditis may develop.

With regard to the type of hydrocephalus, Passot came to the conclusion that it was purely external (hydropisie meningée), firstly from the fact that on lumbar puncture there was an abundant flow of cerebrospinal fluid which relieved the pressure, and secondly because in

one case that was operated on, there was a free flow of cerebrospinal fluid when the dura was incised. Confirmation of this view was obtained in two of my cases in which ventricular tapping was carried out. In Case 4 the ventriculogram was normal. In Case 5 the ventricular pressure was only slightly raised; difficulty was experienced in putting air into the ventricles, and the subsequent ventriculograms were failures. These findings definitely excluded an internal hydrocephalus, and along with a negative Queckenstedt's test and free flow of fluid, pointed to an accumulation of cerebrospinal fluid outside the ventricular system. Davidoff and Dyke, in twelve out of their fifteen cases of serous meningitis, performed pneumo-encephalography. In every case the ventricular system was normal in size, shape and position. The authors comment on the high proportion of their cases in which ventriculography failed to show satisfactory filling, which they attribute to the small size of the ventricle and the high intracranial pressure. They believe that these two factors caused the expulsion of air along the needle-track. These findings are important and support Passot's original contention that the condition is one of external hydrocephalus. They enable a clear distinction to be made between toxic hydrocephalus and the type of arachnoiditis of the posterior fossa which causes an obstruction.

The actual cause of the hydrocephalus may be due to over-production of cerebrospinal fluid, or to some difficulty in absorption of the fluid, or possibly to a combination of these causes. It seems clear that the comparatively rapid disappearance of the papillœdema and raised intracranial pressure that may occur as a result of lumbar puncture, precludes the possibility of an actual pathological obstruction to the absorption of the cerebrospinal fluid. On the other hand, the rapid onset of the condition suggests an over-production of cerebrospinal fluid, and as the choroid plexus may be regarded as the source of the fluid, it may be assumed that some alteration in its function takes place, presumably due to the effects of toxins circulating in the blood-stream.

Summary.

The adjective "toxic" is suggested to describe the hydrocephalus that may follow otitis media, nasopharyngeal, and other sources of infection in young persons.

Five cases are described in which a nasopharyngeal infection seemed to be the causal factor.

The results of treatment by spinal drainage are given.

The differential diagnosis from arachnoiditis and tumours of the posterior fossa is discussed.

Evidence is brought forward in support of the view that the hydrocephalus is of the external type, and that it is caused by an overproduction of cerebrospinal fluid.

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THE AXIS-CYLINDER AS A PATHWAY FOR DYES AND SALTS IN SOLUTION, WITH OBSERVATIONS ON THE NODE OF RANVIER IN THE RABBIT.

BY J. R. PERDRAU.

(From the National Institute for Medical Research.)

THE path followed by certain neurotropic viruses in reaching the central nervous system from the periphery or in infecting a part of that system distant from the portal of entry of the virus (e.g. poliomyelitis) is generally considered to be the axis-cylinder. At any rate such is the obvious interpretation of certain observations in experimental infections (Fairbrother and Hurst, 1930). But no proof has yet been forthcoming that the axis-cylinder and not some other constituent of the nerve fibre is the actual pathway followed by even such a small virus as that of poliomyelitis (size about 10 mμ.).

The following experiments were therefore undertaken in order to determine whether substances easily recognized by their colour can travel along the axis-cylinder in the living animal. In addition, similar experiments were made with pieces of nerves and spinal cord obtained from animals immediately after death.

METHODS.

The sciatic nerve of the rabbit was used for the majority of the experiments, but a few isolated observations were also made on the nerves of frogs, guinea-pigs, &c. The sciatic nerve of a rabbit under deep dial anæsthesia was cut, preferably with a very sharp knife in order to avoid crushing the nerve, and one end of the cut nerve, usually the proximal, for a distance of 5 mm. rested in a solution of the the dye in Ringer's fluid. A piece of glass tubing 10 cm. long, bent to a right angle at a point 2 cm. from one end contained the dye. The short limb was closed by a thin piece of rubber sheeting tied over it and perforated by a short piece of capillary tubing through which the nerve was threaded. It is best to close the free end of the tube to avoid siphoning. The wound can be closed over such an apparatus. Kinking of the nerve or pressure of any kind must be avoided. The dyes used

PLATE VII.

FIG. 1.

FIG. 2.

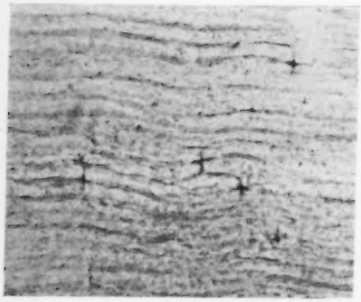

FIG. 3.

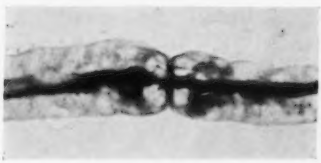

FIG. 4.

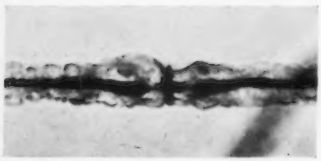

FIG. 5.

FIG. 6.

FIG. 1.—Rabbit sciatic, excised and impregnated through one end only with methylene blue. The nodes are not seen. × 100.

FIG. 2.—Rabbit sciatic, excised and impregnated by cataphoresis with the P.B. mixture (see text). Rings round the myelin sheath at the node. A first stage in the separation of two contiguous segments of myelin. × 450.

FIG. 3.—Rabbit sciatic impregnated in the living animal with the P.B. mixture. Crosses mark the nodes, the internode being only faintly stained. × 220.

FIGS. 4 and 5.—Rabbit sciatic, excised and impregnated by cataphoresis with the P.B. mixture. In fig. 5 the nerve was not fixed with formalin as usual and the myelin is severely damaged. × 450.

FIG. 6.—Same as fig. 5 (not fixed). One segment of the myelin sheath at the node is more heavily impregnated than the other. × 450.

To illustrate paper by J. R. Perdrau.

PLATE VIII.

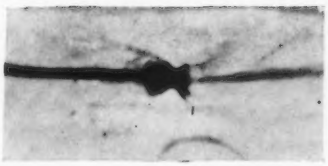

FIG 7.

FIG. 8.

FIG. 9.

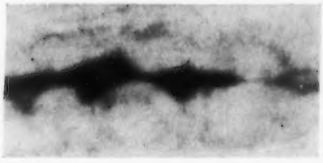

FIG. 10.

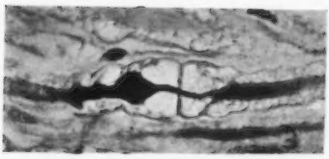

FIG. 11.

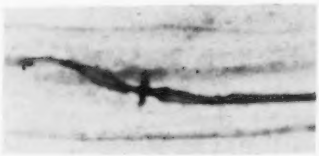

FIG. 12.

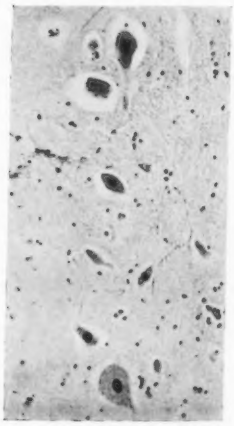

FIG. 13.

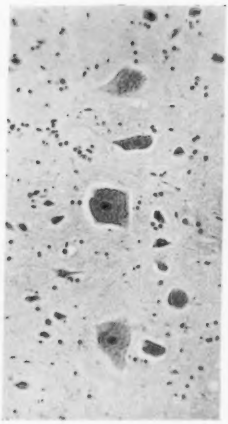

FIG. 14.

FIGS. 7, 8 and 9. Same as figs. 4 to 6, but fixed in formalin. Three nodes at the final stage of separation of two contiguous segments of myelin from each other. × 450.

FIG. 10.—Same as fig. 3. Only half of a "renflement biconique" of Ranvier is seen. × 900.

FIG. 11.—Same as fig. 4. Paraffin section showing thinness of axis-cylinder at the node with a swelling just beyond caused by stretching the nerve. × 450.

FIG. 12.—Same as fig. 3. Swellings on axis-cylinder as the result of stretching a lightly impregnated fibre. × 450.

FIGS. 13 and 14.—Excised piece of spinal cord impregnated by cataphoresis through the sciatic nerve. In fig. 13 the dark nuclei contain Prussian blue, which had not yet reached the cells seen in fig. 14. Counterstained with alum-carmine. × 105.

To illustrate paper by J. R. Perdrau.

have been chiefly methylene blue and acid fuchsin, but it is very difficult to obtain permanent preparations with such easily soluble dyes. The nerves were teased immediately after removal and mounted in melted gelatine with or without a piece of cellophane acting as a coverslip. The gelatine is allowed to dry quickly, at 37° C. for preference.

The Prussian-blue method is far preferable and allows of fixation for any length of time, and sections (frozen, paraffin, &c.) as well as teased preparations are possible. Frozen sections and teased fibres should be mounted in such a way that the whole preparation is dry within a few hours, otherwise the Prussian blue will begin to "run". Paraffin sections can be mounted in balsam in the ordinary way. A counter-stain such as alum carmine, safranin or eosin is sometimes useful.

For the Prussian-blue method mixtures of equal parts of 10 per cent. potassium ferrocyanide and of 10 per cent. iron ammonium citrate in Ringer's fluid were used. Fixation was carried out in 10 per cent. formalin in saline containing a little hydrochloric acid (not more than 1 per cent.).

This mixture of potassium ferrocyanide and iron ammonium citrate (subsequently referred to as the P.B. mixture) has been called true Prussian blue by some. This is erroneous as the Prussian blue is only formed after acidifying the mixture. The substances which are present in the mixture, and which impregnate the nerve, are in true solution and pass through a gradocol membrane of an average pore diameter of 5 mμ. Colloidal Prussian blue purified by dialysis after acidifying with oxalic acid, cannot be substituted for the mixture.

For resected pieces of nerves, still attached or not to the spinal cord, various methods were used. The nerve can be suspended in a tube containing a little of the dye in solution or of the P.B. mixture, and liquid paraffin is floated on top so that only 2 or 3 mm. of the nerve lie in the solution. The liquid paraffin prevents evaporation, especially when the nerve is wrapped in gauze wetted with Ringer's fluid.

For the cataphoresis experiments non-polarizable electrodes were used with a 12 volt battery ($\frac{1}{2}$ to 1 milliamp). The nerve was again kept moist during the whole of the experiment. As all the substances used in these experiments are negatively charged, they were connected up to the kathode. One feature of great importance in all these experiments is that no pressure of any kind should be applied to the nerve. For instance, the pressure produced by a drop of melted vaseline which is allowed to solidify round the nerve in order to obtain a waterproof joint is enough to frustrate the object of the experiment.

The Axis Cylinder.

Both in the living animal and with isolated pieces of nerve, the dye or the P.B. mixture will permeate the axis-cylinder selectively, with great ease at first but more slowly afterwards, for a distance of 4 to 5 cm. in about four hours (Plate VII, fig. 1). The connective tissue sheaths will also take up the dye, the perineurium heavily, but Henle's sheath only lightly. The axis-cylinders do not all take up the dye equally well. As a rule the largest fibres are the most heavily stained whilst the intensity of the colour diminishes the further the dye travels. Little difficulty was therefore encountered in demonstrating that certain substances in true solution travel easily and apparently selectively along the axis-cylinder. In order to make sure that the dye or the P.B. mixture did not reach the axon by any other way, pieces of nerves were firmly ligated at both ends and allowed to soak in the substances used. If the perineurium is intact the axon remains colourless. In Dogiel's method of demonstrating nerves in thin layers of tissues which are immersed in a solution of methylene blue, it is quite likely that the dye has travelled up the axis-cylinder from its cut end.

On the whole, therefore, the results obtained in the experiments now reported agree with the modern view that the consistency of the axis-cylinder is that of a soft jelly (de Rényi, 1929).

Permeation is considerably increased in intensity and in extent by the use of a weak electric current (cataphoresis). Positive results have only been obtained so far with substances in true solution. With colloidal preparations such as Prussian blue and Victoria blue not a trace of impregnation of the axis-cylinder has ever been obtained. Congo red and carminic acid in cataphoresis experiments have given slight staining of the axis-cylinder for a distance not exceeding $\frac{3}{4}$ cm., but these experiments have been too few to allow of any deductions being drawn from them. These colloidal dyes precipitate very quickly in Ringer's fluid, and no better results were obtained when a little protein was added to them. Distilled water as the solvent produces undesirable changes in the nerve fibre.

Nodes of Ranvier.

Apart from the fact that substances in true solution are capable of spreading along the axis-cylinder, some other interesting observations on the nodes of Ranvier were also made, particularly with the P.B. mixture. As already stated, this mixture travels not only along the axis-cylinder, but also along the connective tissue sheaths. The perineurium

is usually an intense blue and is easily dissected off. Henle's sheath is a pale blue and is in sharp contrast with the deeper colour of the axis-cylinder. In cataphoresis experiments the neurilemma and occasionally the network of neurokeratin in the myelin sheath are also faintly outlined.

At the nodes the P.B. mixture has the property of separating any two contiguous segments of myelin from each other, and various stages of this process can sometimes be seen in a single preparation. With methylene blue, on the other hand, one sees only a continuous axis-cylinder without any cross-pieces of any kind (fig. 1), in fact it is extremely difficult in mounted preparations to recognize the site of the nodes. The external outline of the myelin sheath looks continuous without even a depression at the nodes.

With the P.B. mixture the junction between any two segments of myelin is quickly revealed, because the joint is rapidly permeated both from the side of the axis-cylinder and from Henle's sheath, so that on acidification the site of the node becomes obvious. A depression appears on the surface of the myelin sheath and a blue ring is often seen there (Plate VII, fig. 2). At the same time the mixture extends into the joint from the axis-cylinder and if this has gone far enough the classical appearance obtained with silver nitrate is reproduced (fig. 3). A longitudinal section of the nerve at this stage shows blue crosses at the nodes with an unstained or lightly stained internode. This does not mean that the axis-cylinder at the internode does not contain the P.B. mixture, but rather that the acid has not been able to penetrate so far and precipitate the Prussian blue.

The further stages of what happens at the nodes are best observed in cataphoresis experiments. The cross-pieces thicken and shorten (figs. 4 and 5) as the depression on the surface deepens until ultimately the contiguous surfaces of any two adjoining segments of myelin become separated (Plate VIII, figs. 7 to 9). These surfaces now adopt a rounded appearance and become more intensely impregnated. A careful study of the nodes at this stage gives the impression that the myelin sheath is not so firmly adherent to the axon at the node as it is at the internode and is loosened from its attachment by the P.B. mixture. One gains an impression of two funnels facing each other with the axis-cylinder in the centre. This appearance may be an exaggeration of the "renflements biconiques" of Ranvier, which are frequently seen in these preparations and which may be an earlier stage of one and the same process, that is to say, of the lifting of the myelin sheath from the

axis-cylinder at the node. The "renflement biconique" of Ranvier may sometimes consist of a single cone (fig. 10), one segment of myelin having apparently lifted up from the axis-cylinder before its immediate neighbour.

Another point which is well demonstrated in these preparations is the thinness of the axis-cylinder at the node (fig. 11).

The accompanying photographs do not give the gradations in colour which one sees under the microscope since very thin preparations are only possible after embedding in paraffin wax and also because cellophane is quite unsuitable for photomicrography. Fixation in formalin is responsible for the small cross-sectional area of the axis-cylinder as compared with that of the myelin sheath.

Certain artifacts are inevitable, especially owing to the necessity of mounting in gelatine. The outline of the myelin sheath in unfixed preparations (figs. 5 and 6) is often wavy. Swellings on the axis-cylinder (figs. 11 and 12) are common in teased preparations, especially in lightly impregnated fibres. A heavily impregnated fibre such as one obtains in cataphoresis experiments usually retains a uniform outline (figs. 6 to 9) even after teasing. These swellings, which are well known with other methods of demonstrating the axis-cylinder are never seen in the thin nodal portion where the axis-cylinder is denser than elsewhere (de Rényi, 1929) and is therefore more resistant to stretching. The incisures of Schmidt-Lantermann are not revealed in these preparations, but the neurokeratin network, as already stated, is often faintly outlined in heavily impregnated fibres.

On the whole, therefore, by the use of the Prussian-blue method the underlying principle on which the nodes of Ranvier in the rabbit are constructed can be shown to be similar to that which obtains in the frog. In the latter the failure of the segments of myelin to meet at the node as well as the incisures of Lantermann can be easily demonstrated in a teased preparation.

Many of the stages described and figured in this paper are well known. That these stages are a continuous process as the result of certain manipulations adopted for the demonstration of the node it is the object of this paper to show.

Effect on the Nucleus of the Nerve Cells.

If a piece of spinal cord (e.g. lumbar) with one anterior root still in position is impregnated through that root by cataphoresis, the Prussian blue will be found on acidifying to have accumulated almost exclusively

in the nuclei of healthy cells of the anterior horn which have not been altered by the conditions of the experiment. The axis-cylinder has been traced almost continuously on rare occasions from the surface of the cord to the cell. The chromatin in these cells is intensely coloured (compare figs. 13 and 14) but the nucleolus and cytoplasm as well as the tigroid substance remain unstained and can be counterstained with alum carmine, pyronin, etc. Cells which are obviously altered as the result of the various manipulations are often stained a uniform blue.

If a piece of cervical cord (e.g. C_3) is used where the anterior and posterior roots unite immediately on emergence from the cord and where the posterior root ganglion is firmly adherent to the cord, the nuclei of the ganglion cells, as a rule, do not take up the P.B. mixture, but the cells of the cord itself do. The explanation for this difference in behaviour may be found in the peculiar mode of entry and of exit of the axis-cylinder from the cells of the ganglion, so that the P.B. mixture rarely reaches the neighbourhood of the nucleus. Whatever the explanation may be for the presence of the Prussian blue in the nucleus, it is not suggested here that the axis-cylinder has any direct connection with the nucleus. It may be mentioned incidentally that the presence of neurofibrils in the axis-cylinder of the rabbit is not revealed by these methods of impregnation.

Conclusions.

(1) Dyes such as methylene blue and acid fuchsin and also a mixture of potassium ferrocyanide and iron ammonium citrate travel up the axis-cylinder in the living rabbit as well as in resected pieces of nerves. Cataphoresis greatly enhances the process, but the slightest pressure on the nerve or simple kinking stops the impregnation.

(2) Only salts in true solution behave in this way. Colloidal substances tested up to now, such as Prussian blue and Victoria blue, do not.

(3) The mixture of potassium ferrocyanide and iron ammonium citrate, in contradistinction to methylene blue, reveals the nodes of Ranvier, and if its action is sufficiently prolonged it leads to a separation of the myelin sheath into sections which meet at the nodes, where the myelin is less firmly adherent to the axis-cylinder than it is at the internode.

(4) The "renflement biconique" of Ranvier as well as the cross are probably early stages of this process of separation.

(5) The modern conception of the axis-cylinder as a soft jelly, except

at the node where it is denser and thinner, is supported by these observations.

(6) If the nerve cells of the spinal cord are impregnated through their axis-cylinders by the Prussian blue method reinforced by cataphoresis the nuclei only will be coloured blue. In the posterior root ganglia the nucleus like the rest of the cell body is usually colourless. In altered cells the Prussian blue may be found in both the nucleus and the cytoplasm.

I am indebted to Dr. C. Todd for much help and advice and to Mr. Barnard and his assistants for the photomicrographs.

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THE ORIGIN OF THE RAISED PRESSURE OF THE CEREBROSPINAL FLUID WHICH ACCOMPANIES SUBTENTORIAL TUMOURS.

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IT has been known since the classical experiments of Dandy and Blackfan [9] that obstruction of the aqueduct of Sylvius causes an accumulation of cerebrospinal fluid and a dilatation of the chambers and channels anterior to the block. Dandy and Blackfan were also able to produce hydrocephalus by occluding the subarachnoid space of the midbrain at the level of the tentorium cerebelli. The hydrocephalus developed as rapidly as that which followed occlusion of the aqueduct.

Although an intracranial tumour may occasionally invade and directly occlude a main cerebrospinal fluid channel, such an occurrence is generally admitted to be unusual.

Hodgson [14] investigated twenty-four cases of subtentorial tumours by combined ventricular and lumbar puncture. He found that "sixteen, or two thirds, showed block in some degree and one third did not show any block. Of twenty-one supratentorial tumours block, on the contrary, was absent in nineteen, slightly questionable in one, and definitely present in only one of these cases, a pinealoma." The absence, however, of a communication between the ventricular and the lumbar needle does not, as Stopford [20] has pointed out, prove the existence of an obstruction to the aqueduct; the obstruction may be at the foramen magnum. Stopford investigated a series of five subtentorial tumours. In each instance the signs of intracranial pressure had appeared early and were profound. He concluded, as a result of a careful examination of the brains after death, that it was unlikely that there had been any obstruction to the normal circulation of cerebrospinal fluid in at least four of the five cases.

Masserman and Schaller [17] quote a personal communication from F. L. Reichert in which the latter worker states that he had occasion to insert ventricular, cisternal, and lumbar needles preceding a craniotomy on a patient with a tumour of the brain. The site of the tumour and

the pressure of the cerebrospinal fluid were not stated. Reichert, however, "noted that the horizontal pressure readings at the three loci remained equal under various manipulations."

Masserman and Schaller studied the mechanical effect of artificial tumours in different parts of the brain on intracranial hydrodynamics. Observations were made on three cadavers. The intracranial pressures were maintained by artificial means. The tumours were produced by injection of 20 to 40 c.c. of melted paraffin wax in various regions inside the skull. The distortion so produced in the frontal or occipital regions had no apparent effect on the fall of ventricular or cisternal pressure when the fluid was removed by lumbar tap. "When 30 c.c. of wax were injected into the left cerebellar lobe, a partial block between the ventricular and lumbar spaces was effected. Subsequent examination showed the paraffin to have forced the left cerebellar lobe down against the bulb, partially obliterating the fourth ventricle and basal cistern." Encephalograms revealed no evidence of elevation of the tentorium.

According to Paton and Holmes [19], the papillœdema associated with cerebral tumours is caused by a compression of the central vein of the retina and the accompanying lymphatics as they pass from the optic nerve across the subarachnoid space of the optic sheath. They believe that the vessels are compressed as a result of the raised pressure of the cerebrospinal fluid in the subarachnoid space of the optic sheath. It would seem highly improbable that a raised cerebrospinal fluid pressure could be maintained in this space unless it were in communication with the ventricular system (Brain and Strauss [8]). It would appear justifiable to conclude, on the basis of this theory, that the subarachnoid space of the optic nerve must have been in communication with the ventricular system during some period in the development of all intracranial tumours which are accompanied by papillœdema.

Baurmann [1] has reported experiments which would seem to support the conclusion of Paton and Holmes that the central vein of the retina is compressed as a result of the raised pressure of the cerebrospinal fluid in the subarachnoid space of the optic sheath. He found a direct relationship between the pressure of the cerebrospinal fluid and the pressure in the veins on the nerve head. He took as his criterion of the venous pressure the intra-ocular pressure at which the veins on the nerve head first began to pulsate. The intra-ocular pressure was raised by pressure on the eyeball with a gauge of the type devised by Magitot.

Duke-Elder [11] has criticised all the methods in which venous

pulsations are used as a criterion of venous pressure. He considers that venous pulsations in the eye are a complicated phenomenon not directly related to the pre-existing intra-ocular pressure.

Baurmann's experiments have recently been repeated on animals by Gibbs [13], who employed a slightly different technique. Baurmann's findings were confirmed. Gibbs concluded, however, that "although it is possible that Baurmann did not measure the true venous pressure, it is certain that he measured something that is a direct and simple function of the venous pressure." It is noteworthy that Magitot [15], and Berens, Smith and Cornwall [7], claim to have found a relationship between the diastolic pressure in the central artery of the retina and the pressure of the cerebrospinal fluid.

The experiments which are to be described were undertaken in an attempt to produce artificial intracranial tumours in dogs and to observe their influence on the pressure and the circulation of the cerebrospinal fluid and on the venous pressure in the torcular. These experiments were limited to a study of subtentorial tumours.

Experimental Technique.

The dogs employed in these experiments were mongrels about 2 to 3 years old and weighing from 7 to 8 kilogrammes. Considerable difficulty was at first encountered in devising a suitable technique. Finally, however, the following method was evolved and employed throughout the experiments.

The animals were anæsthetized with intratrachial ether. A transverse incision was made through the skin a short distance behind the external occipital protuberance and the posterior aspect of the occipital bone exposed by a vertical incision along the line of the nuchal ligament. The muscles were retracted with the aid of a mastoid retractor. In the dog, the inferior vermis of the cerebellum is a relatively prominent structure which rests in a depression in the occipital bone called the fossa vermiana. The fossa vermiana usually gives rise to a definite protuberance on the external aspect of the occipital bone which is visible at the bottom of the wound when the muscles are separated. An attempt was made in all experiments to produce a mid-line tumour either in the vermis itself or directly behind the inferior vermis.

A small drill hole is made with a dental bur through the lower part of the protuberance which corresponds with the fossa vermiana. In this region the bone is relatively thin. The aperture is enlarged until a little more than $\frac{1}{8}$ in. in diameter. This can usually be accomplished

without injury to the dura which readily separates from the bone. It is, of course, necessary to open the dura if a tumour is desired in the substance of the cerebellum. Tumours in the substance of the cerebellum, however, were difficult to produce successfully and in nearly all the experiments the foreign matter was introduced between the dura and the bone. The tumours were, therefore, extradural in situation.

The most suitable foreign matter for the production of the tumours was ordinary surgical cotton wool impregnated with wax. It was prepared and employed in the following manner. A quantity of paraffin wax melting at 49° C. is placed in an evaporating dish in an incubator set at 55° C. Pledgets of cotton wool, together with a few crystals of carbolic acid, are placed in the melted wax. When required for use, a piece of wool is taken from the dish, as much as possible of the wax squeezed out and the mass shaped while hot to the desired size. The mass is prevented from setting by constant kneading with the fingers. Small pieces of convenient size are now torn from it and are passed with fine forceps through the hole in the occipital bone until the whole of the mass has been treated in this way. It is unnecessary to close the hole in the bone, for the tumour displays no tendency to extrude itself. The muscles are now brought together and the wound closed in the usual way.

With regard to the quantity of material introduced into the cranium, a tumour 0·6 to 0·8 c.c. in volume was found to be the optimum for a dog of the size employed in these experiments. It is interesting to note that the average capacity of the infratentorial space in the fresh skull of a dog weighing 8 kg. is approximately 12 c.c., while the total intracranial capacity is about 75 c.c.

Under ordinary circumstances, the animal appears normal after it has recovered from the anæsthetic and remains symptomless until it is killed six days later. If, however, the tumour has been made excessively large or the cerebellum has been injured during its introduction, the animal may present varying degrees of ataxia. The ataxia is generalized and involves all four limbs and the head. In mild cases the animal walks with its feet set widely apart and there are oscillatory movements of the head. In such a case the condition generally clears up completely in twenty-four to forty-eight hours. In a more severe case the animal is completely ataxic and unable to stand or to support itself in any way. All animals which were unable to stand or walk after a recovery period of twenty-four hours were promptly killed, for they were obviously unsuitable for prolonged observation. In two instances

sudden death occurred shortly after the tumour had been introduced. It was considered that the excessive bulk of the tumour had probably led to medullary compression. Occasionally the conduct of the animal made it apparent that it was suffering from severe headache. This was usually observed during the period which immediately followed operation. The headache was considered to be caused by local tension in the dura under the tumour, for it bore no relation to the pressure of the cerebrospinal fluid. Vomiting was not observed in a single instance. An ophthalmoscopic examination was made from time to time in an attempt to detect the onset of papillœdema. Papillœdema was never observed, although the pressure of the cerebrospinal fluid was over 400 mm. normal saline in a number of animals.

At post-mortem examination five to six days after operation, the waxed wool is found to have formed a compact almost spherical tumour which shows little tendency to flatten itself against the bone but projects well forward into the cerebellum. The residual wax prevents the tumour from becoming sodden with blood and exudate. The tumour is adherent to the dura. There is rarely any bleeding although a little fibrinous exudate may be present. On removing the tumour, a circular depression about 1 cm. in diameter and $\frac{3}{4}$ cm. in depth is observed in the region of the inferior vermis and the adjacent lateral lobes of the cerebellum. The dura underlying the tumour is not adherent to the arachnoid. The arachnoid and the cerebellar cortex immediately beneath the tumour generally appeared normal on naked-eye inspection. The subarachnoid space in this region is almost always free from blood although small subpial hæmorrhages may sometimes be visible. Occasionally a small area of hæmorrhagic softening was present in the interior of the cerebellum. This and the subpial hæmorrhages were probably a result of the trauma which accompanied the introduction of the tumour.

The arachnoid, the pia and the brain substance are to a great extent protected from any irritant action by placing the tumour between the dura and the bone. The cerebrospinal fluid from the cisterna magna, when examined four to six days after operation, was normal in its cell content. Occasionally a slight increase in the total protein content was observed. It is interesting to note that Indian ink, introduced into the subarachnoid space through a needle in the cisterna magna at a pressure only slightly above that of the cerebrospinal fluid, usually found its way to the subarachnoid space in the immediate vicinity of the tumour, although it rarely entered the subarachnoid space directly below the tumour. This was regarded as providing evidence that the tumours

did not initiate a spreading obliterative process in the post-cerebellar subarachnoid space. A histological examination of the brains failed to detect any evidence of an inflammatory lesion. Occasionally the arachnoid underlying the tumours presented a slight degree of cellular proliferation. The pia was unchanged. Subpial hæmorrhages when present in this region, were observed to be undergoing changes common to hæmorrhages in the brain. There was rarely any evidence of œdema. The brain and its coverings were unchanged in all other regions.

A careful comparison of brains fixed *in situ* with control specimens never showed the tentorium to be more than slightly raised. The tentorium of the dog is partly ossified. It contains a triangular plate of bone. The apex of the triangle is truncated and forms the posterior border of the incisura tentorii. Its base is firmly attached to the occipital bone along the line of lateral sinuses, where it extends almost as far forward as the petrous-temporal bone. Only the antero-lateral portions of the tentorium are membranous. The ossified portion of the tentorium consists of dense non-flexible bone. Its flexibility was tested on fresh unfixed skulls from which the brain had been removed piecemeal. Pressure was exerted from below and also from above. The bone remained perfectly rigid. If a considerable degree of force was applied, the bone was found to snap rather than bend. It is, of course, conceivable that constant pressure applied for several days may cause some displacement of the bone. The tumours were situated below the ossified portion of the tentorium but were separated from actual contact by part of the cerebellum (fig. 1). The falx cerebri of the dog is not ossified.

An upward displaced tentorium would naturally carry with it the straight sinus and the termination of the great vein of Galen. Careful dissections of brains containing subtentorial tumours which had been fixed *in situ* after injection of the venous system with a carmine gelatine mass, failed entirely to provide evidence that the flow of blood through the great vein of Galen had been obstructed at any point on its course. A careful examination was also made of brains containing a subtentorial tumour which had been fixed *in situ*, but in which the venous system had not been injected with a carmine gelatine mass. It was realized that no matter how carefully the injection be made, there is a risk that the pressure which it is necessary to employ may be sufficient to overcome and to obscure a moderate degree of venous obstruction. Here again, however, no evidence of venous obstruction could be detected.

In a number of experiments the introduction of the tumour was

followed by clotting in the torcular. The results from all these experiments were discarded, for it is known that an obstruction to the venous blood in the torcular causes changes in the pressure of the cerebrospinal fluid [5, 6]. Some difficulty was experienced at first in discovering an explanation for this venous clotting, which at times was very troublesome. It was found, after a number of fresh dogs' skulls had been

FIG. 1.—A considerably enlarged and untouched photograph of a sagittal section through a brain (Dog No. 20, Table I), containing an artificial subtentorial tumour. The section has passed to the left of the falx cerebri. The brain was fixed in situ and was then removed from the skull. It is improbable, therefore, that the various structures have suffered any displacement. A small quantity of waxed wool has been lost from the posterior aspect of the tumour. The dura underlying the tumour is clearly visible. The dark area below the apex of the tumour is an unusually large subpial hæmorrhage. The great vein of Galen and the straight sinus (the latter has been opened) are clearly visible and it is evident that these structures are in no way compressed. The cerebellum is displaced forward and is indented by the anterior border of the tentorium. A comparison with control specimens reveals no evidence of elevation of the tentorium.

examined, that although the anterior, the posterior and the lateral walls of the torcular consist of strong bone, the floor is often formed by an extremely thin semi-transparent shell of bone. A portion of the cerebellum lies directly below the torcular, and the dura of the posterior fossa is therefore in contact with this thin layer of bone which forms

the floor of the torcular. Not infrequently the tumour causes the dura to be stripped from the bone in this region. Under these circumstances, the tumour lies directly below the floor of the torcular and is only separated from the blood in its interior by an extremely thin layer of bone and by the endothelial lining of the sinus. It is not surprising, therefore, that reactive processes are frequently set up in the endothelium which ultimately lead to clotting.

Clotting in the torcular can generally be avoided by taking the precaution to place the tumour so that it does not exert pressure on the bone in this region.

It must be admitted at the outset that tumours produced in this manner cannot be considered identical with neoplastic tumours. They differ mainly in the following ways: (1) While neoplastic tumours may suddenly increase in size as a result of bleeding into their substance or of the onset of acute œdema, their growth for long periods is often gradual and continuous. It is thus possible for them to attain a size which is relatively much greater than that of the maximum quantity of foreign material which can suddenly be introduced into the cranium without serious interference with function; (2) artificial tumours probably produce their maximum effect very shortly after introduction. These effects will become less marked as the brain substance gradually accommodates itself to the mass. This is the reverse of the process which generally obtains with neoplastic tumours. It was the custom, for this reason, to examine the intracranial pressures not later than six days after the introduction of the tumours.

This method of producing intracranial tumours has, therefore, serious limitations. Nevertheless it was hoped to obtain effects which might bear a general resemblance to those produced by neoplastic tumours.

The Effect of Artificial Subtentorial Tumours on the Intracranial Pressures.

On the fifth or sixth day after the introduction of the tumours the animals were anæsthetized with ether and a reading taken of: (1) The cerebrospinal fluid pressure in the cisterna magna; (2) the venous pressure in the torcular Herophili; (3) the arterial pressure in the femoral artery. The methods employed to record these pressures have been described in detail in an earlier paper [5]. The results obtained from twenty-one animals are indicated in Table I.

The tumours were extradural in situation and were produced in the manner which has already been described with the exception of Dog

No. 1. In this animal the tumour was intracerebellar and was formed by injecting paraffin wax into the substance of the cerebellum.

(1) *The pressure of the cerebrospinal fluid in the cisterna magna.*—It is difficult to assign an upper limit for a normal cerebrospinal fluid pressure; the pressure varies over a wide range in different animals. The nature of the anæsthetic and the mode of its administration also have a definite influence on the height of the pressure [21, 17]. It would seem that a pressure which exceeds 200 mm. normal saline may generally be regarded as abnormally high. This conclusion has been reached after a study of the cerebrospinal fluid pressure in a large number of normal animals under ether anæsthesia. A standard technique was employed throughout the experiments.

TABLE I.

The intracranial pressures in twenty-one cases of artificial subtentorial tumour. The volume of the tumours was determined after death, and the figures indicate the volume of waxed wool introduced into the cranium. No account, therefore, is taken of exudate or of local œdema of the brain which, when present, will increase the potential volume of the tumour. The pressure of the cerebrospinal fluid and the venous pressure in the torcular are recorded in millimetres of normal saline solution, that in the femoral artery in millimetres of mercury.

Dog No.	Cerebrospinal fluid pressure	Venous pressure in torcular	Systolic pressure in femoral artery	Hydrocephalus	Volume of tumour in c.c.	Post-operative duration of life in days
1	450	85	100	Moderate	1·0	6
2	290	60	110	Moderate	0·8	5
3	300	105	120	Moderate	0·6	5
4	270	90	120	Moderate	0·6	6
5	200	80	140	0	—	6
6	350	105	140	0	0·6	5
7	450	90	130	0	0·7	6
8	280	70	130	0	—	5
9	140	80	130	0	0·4	6
10	120	110	125	0	0·4	8
11	420	120	125	0	0·8	6
12	270	90	110	0	0·7	6
13	270	120	125	0	—	6
14	320	110	130	0	0·7	6
15	350	50	110	0	0·8	6
16	210	120	120	0	0·5	6
17	420	115	120	0	0·7	6
18	330	90	110	0	0·8	6
19	410	80	130	0	0·8	6
20	370	85	120	0	0·6	6
21	280	70	120	0	0·6	6

It will be observed from Table I that the subtentorial tumours have caused in nearly every instance a pronounced increase in the pressure of the cerebrospinal fluid in the cisterna magna. It is noteworthy that it

was possible to obtain a reading from the cisterna magna in all experiments. In the later experiments it was the custom to measure also the pressure of the cerebrospinal fluid in the lateral ventricles.

This was easily accomplished by boring a hole through the skull over a lateral ventricle. A gauge 18 needle was then passed down through the dura into the ventricle. The needle was connected with a manometer and the pressure recorded in the ordinary way. The position of the needle and the depth to which it should be introduced were determined from measurements on heads previously fixed in formalin. It was necessary to employ a clamp fixed to the head of the animal in order to maintain the needle steady after its introduction.

The ventricular and the cisternal pressures were always identical. Changes produced in the pressure in the cisterna magna were followed by corresponding changes in the intraventricular pressure, and vice versa.

According to Masserman and Schaller [16], the ventricular-subarachnoid system of the dog differs from that of man in not being able to transmit readily changes in pressure from one portion to another. "Thus if one suddenly raised a dog's ventricular pressure to 75 cm. water, the cisternal and lumbar pressures would climb to the level after a variable interval. Conversely, if a rapid lumbar tap were then done, the curves of intraventricular and intracisternal tension would show a lag of from one to seven seconds before beginning a decline parallel to that of the pressure in the lumbar sac." The lag described by Masserman and Schaller was observed in the animals with subtentorial tumours. It was of varying duration but did not show any marked deviation from that encountered in normal animals. It would appear, therefore, that the tumours had not caused an obstruction of any consequence to the aqueduct of Sylvius.

(2) *Hydrocephalus with artificial subtentorial tumours.*—Hydrocephalus was found in dogs Nos. 1, 2, 3 and 4. It is remarkable that these cases occurred at the beginning of the investigation and succeeded each other. Since then, hydrocephalus has not been encountered in a single experimental animal.

In one instance the tumour was intracerebellar and consisted of wax. In the remaining three cases the tumours were of standard size and were extradural in situation. The technique employed differed in no way from that used in the rest of the experiments. The animals presented no abnormal signs during the post-operative period. It is noteworthy that the pressure of the cerebrospinal fluid in the cisterna

magna at the termination of the experiment, was no greater than that in cases uncomplicated by hydrocephalus (Table I). The dilatation of the ventricles was moderate in degree and involved the lateral and the third ventricles. There was, however, slight but definite dilatation of the aqueduct and of the fourth ventricle in all four brains. The cerebrospinal fluid was normal in its cell and protein content, and an histological examination of the brains and of their coverings revealed no evidence of an inflammatory lesion. It is regrettable that the intraventricular pressure was not recorded in any of these animals. It is noteworthy, however, that Indian ink introduced into the cisterna magna in two of these animals spread over the entire cerebral cortex. Indian ink was not introduced in the remaining two cases.

(3) *The venous pressure in the torcular of Herophili.*—The venous pressure in the torcular was always within normal limits. The effect of clotting in the torcular on the pressure in the superior longitudinal sinus will be considered later.

(4) *The systolic blood-pressure in the femoral artery.*—The tumours were without apparent influence on the systolic pressure in the femoral artery.

(5) *The introduction of Indian ink into the cisterna magna.*—A suspension of Indian ink in normal saline solution, about one part of Reeves' Indian ink to four parts of saline solution, was introduced into the cisterna magna before killing the animals. The following procedure was employed when introducing the ink: The suspension, prepared as indicated, was placed in a burette connected with a needle in the cisterna magna. It was the custom to employ for this purpose the needle which had been used to record the pressure of the cerebrospinal fluid. The fluid column in the burette was set either at the exact pressure level of the cerebrospinal level or at a level some 10 to 20 mm. higher. The first method was the method of choice. In this method it was hoped that the minor fluctuations in the pressure of the cerebrospinal fluid which are constantly taking place, would permit some of the suspension to enter the cisterna. It should be borne in mind that if a very small quantity of a relatively strong suspension of Indian ink succeeds in entering the cisterna magna, it will be sufficient to colour, almost immediately, the whole of the cerebrospinal fluid in its interior. The introduction of large quantities of Indian ink is, therefore, unnecessary. The obvious objection to the second method is that a pressure higher than that of the cerebrospinal fluid is employed in order to introduce the ink. In actual practice, however, this method is

probably very similar to the first. The results were identical whichever method was employed.

Replacement methods were also tried, but in view of the observations of Masserman [18] on the effects of drainage of the cerebrospinal fluid on the capacity of the subarachnoid space, they were abandoned as unsatisfactory.

The Indian ink was introduced for periods varying from one to two hours. The volume of fluid introduced varied considerably; good results could be obtained with 1·0 c.c. or even less. As already indicated, it is neither necessary nor desirable to introduce large quantities of the suspension. A careful watch was maintained on the blood-pressure reading in the femoral artery throughout the whole of the experiments. The experiments were discontinued and the readings discarded when the blood-pressure was not maintained.

The animals were killed without disturbing the position of the head by severing the carotid arteries. It was important to remember to cease introducing the Indian ink and to withdraw the needle before killing the animal. The head was removed from the body, the cranium opened and the brain and its coverings fixed *in situ* in isotonic formol saline solution. Occasionally the head was injected with formol saline solution through the carotid arteries. Throughout the whole procedure care was taken to maintain the head with the vertex uppermost. The Indian ink was found to have spread over the cerebral cortex and to have reached the superior longitudinal sinus in every instance when the brains came to be examined. The ink passed freely into the spinal subarachnoid space but only entered the ventricular system in one or two instances.

Similar experiments were conducted on animals without subtentorial tumours. The experiments failed to elicit any difference in the rate of spread of the Indian ink in the normal and in the animals possessing a subtentorial tumour. The following experiment was performed in a number of animals with a subtentorial tumour to exclude the possibility that the spread of Indian ink over the cortex was an agonal or a post-mortem phenomenon.

After the ink had been introduced for an hour, a small trephine hole was made over the convexity of a cerebral hemisphere at a point just external to the superior longitudinal sinus. The ink could generally be seen in the subarachnoid space through the dura. When, however, the dura was opened, the ink was invariably visible in the sulci. These experiments would seem to exclude the possibility that the ink had

spread to the subarachnoid space of the convexity of the cerebral hemispheres during the agonal state.

It would seem desirable, at this stage, to consider briefly the possible means by which the Indian ink introduced into the cisterna magna may spread over the cerebral cortex.

(1) The ink will be transported along with the cerebrospinal fluid if this fluid is circulating.

(2) The ink will also spread by simple diffusion. This process, however, will be most evident in the large cisternæ.

(3) The ink may also be dispersed throughout the entire subarachnoid space in the following manner. The volume of the brain at any given moment depends upon a number of factors. For example, a sudden fall in the systemic blood-pressure is followed by a marked shrinking of the brain. Under these circumstances Indian ink will flow from the burette into the subarachnoid space. If, however, the arterial pressure returns to its previous level, most of the ink will be forced out again into the burette. The area coloured by the ink will, nevertheless, have increased considerably. It is obvious that a repetition of this process will gradually cause the whole of the subarachnoid space to be coloured by the ink. It is well known that the volume of the nervous system can be influenced by variations in the intracranial venous pressure or in the osmotic pressure of the blood. Although stringent precautions were taken to maintain conditions as standard as possible throughout the experiments, it is difficult to be absolutely certain that they were entirely successful in any single instance.

It would appear, therefore, that although the introduction of Indian ink into the cisterna magna may be a suitable method for detecting a complete block to the circulation of the cerebrospinal fluid, it is of doubtful value when employed to detect an incomplete or a functional block. An interference with the circulation of the cerebrospinal fluid, brought about by a displacement of the brain, may be regarded as a functional block. It is probable that under these circumstances the obstruction is frequently incomplete or intermittent.

Conclusions based on observations on the circulation of Indian ink may, therefore, be accepted only with the greatest reserve.

(6) *The intracranial pressures associated with subtentorial tumours in which clotting has occurred in the torcular.*—Clotting in the torcular, as already indicated, was a troublesome occurrence. The clot never extended into the superior longitudinal sinus. The straight sinus was always free from clot. Occasionally, however, the whole of the lateral

sinuses were occluded. The venous pressure in the posterior end of the superior longitudinal sinus tended to approximate and sometimes to exceed that of the cerebrospinal fluid. Not infrequently, however, the pressures were identical. The intraventricular pressure was always identical with that in the cisterna magna. The instability of the intracranial pressures was the most characteristic feature of these cases. The cerebrospinal fluid pressure and the pressure in the superior longitudinal sinus showed a marked tendency to fall and to assume a lower level as the anæsthesia was continued. The effect of venous obstruction on the pressure of the cerebrospinal fluid has, however, been described in earlier publications [5, 6] and need not be reconsidered here.

Discussion.

A method has been described by which artificial subtentorial tumours can be successfully produced and their effects studied in dogs. Attention has already been drawn to the limitations of the method and it has been pointed out that the tumours can be expected to have effects which resemble only in a very general way those of neoplastic tumours.

We are now in a position to consider whether these experiments help in any way to explain the origin of the initial rise in the pressure of the cerebrospinal fluid in cases of neoplastic tumours. It is proposed to consider the possible modes by which an experimental tumour may bring about an increase in the pressure of the cerebrospinal fluid.

(1) The tumours may have irritated the coverings of the brain and induced a condition of sterile meningitis. The raised pressure of the cerebrospinal fluid may, therefore, be merely an expression of meningitis and may have no direct connection with the tumours. This possibility merits careful consideration, for the validity of the remarks which are to follow depends upon its elimination.

(2) The actual mass of the tumour may cause a permanent increase in the intracranial pressure by occupying a large proportion of the intracranial cavity.

(3) The tumour may cause an increased production of cerebrospinal fluid either: (*a*) By causing a state of increased venous pressure in the choroid plexuses; or (*b*) in some manner still undetermined. It is obvious that the pressure of the cerebrospinal fluid will not be raised if the absorption mechanism is able to deal with the excess of fluid.

(4) The tumour may interfere with the absorption of the cerebrospinal fluid in the following ways: (*a*) It may cause a main cerebrospinal fluid channel to be obstructed and thus prevent the fluid from reaching

the subarachnoid space of the cerebral hemispheres; (*b*) the tumour may raise the tentorium and cause the cerebral hemispheres to be displaced upwards against the vault of the skull. This may lead to a diminution in the rate of absorption of the cerebrospinal fluid from the whole of the subarachnoid space of the convexity of the cerebral hemispheres; (*c*) it may raise the intracranial venous pressure and thus interfere with the absorption of the fluid into the blood-stream.

It is proposed to discuss each of these possibilities in turn :—

(1) The tumours were foreign bodies and as such were bound to produce some degree of local irritation. In order to reduce the risk of irritation of the arachnoid and the pia to a minimum, cotton-wool impregnated with paraffin wax was employed to form the tumours and the tumours themselves were placed outside the dura. It has been pointed out that an examination of the cerebrospinal fluid never provided evidence of a pleocytosis, although there was occasionally a slight increase in total protein content. Indian ink introduced into the cisterna magna spread to the very margin of the tumour and occasionally it was observed to enter the subarachnoid space immediately underlying it. A careful histological examination of the brains failed to detect evidence of an inflammatory lesion and the arachnoid and pia underlying the tumours never presented more than a slight degree of cellular proliferation.

We can, therefore, exclude this possibility with some degree of confidence.

(2) A tumour of a given size which caused, when placed below the tentorium, a marked increase in the pressure of the cerebrospinal fluid, had little or no effect when placed above the level of the tentorium. It is improbable, therefore, that the proportion of the intracranial cavity occupied by the tumour is a determining factor, at all events during the initial stages of the syndrome.

(3) (*a*) No evidence could be obtained that the tumours caused either the great vein of Galen or the straight sinus to be obstructed. It is evident from Fig. 1 that the great vein of Galen is in no way compressed. Experimental evidence [3, 4, 5, 6] has been presented elsewhere which suggests very strongly that venous congestion of the choroid plexuses does not cause any increased production of cerebrospinal fluid.

(*b*) The suggestion that the tumour may cause an increased production of cerebrospinal fluid, in some manner still undetermined, is certainly justifiable in view of our ignorance of the mechanism by which

the cerebrospinal fluid is normally produced. No useful purpose will be served, in the entire absence of data, by speculating as to the possible means by which this could be effected.

(4) (*a*) The pressures of the cerebrospinal fluid in the lateral ventricles and in the cisterna magna were always identical. Moreover, pressure changes in the cisterna magna were followed by corresponding changes of pressure in the lateral ventricles, and *vice versa*. A careful examination of brains in which Indian ink had been allowed to circulate for varying periods of time revealed no evidence that the ink had been held up in any particular situation. No demarcation line was ever observed. It must be admitted, however, that although these observations suggest very strongly that there was no complete block to the circulation of the cerebrospinal fluid between the cisterna magna and the base of the brain, they do not exclude the possibility of a partial or an intermittent obstruction in this region. Attention, however, has already been drawn to the fallacies which are attendant on the Indian ink method of investigating the circulation of the cerebrospinal fluid.

(*b*) We have now to consider the possibility that the tumours may have raised the tentorium and caused the cerebral hemispheres to be displaced upwards against the vault of the skull. It is conceivable that this may interfere with the passage of the cerebrospinal fluid over the cerebral cortex and so lead to a diminution of absorption. It is noteworthy that the occurrence of papillœdema with subtentorial tumours in man could perhaps be accounted for on such a basis.

Elsberg and Silbert [12] have shown by means of encephalograms in the human subject that a tumour of one cerebellar hemisphere tends to produce a greater dilatation of the opposite lateral ventricle than of the ventricle of the same side. A unilateral cerebellar tumour or a tumour of the cerebellar-pontine angle often produces distortion of the posterior horn of the homolateral ventricle in an upward, forward and outward direction. Stopford has drawn attention to the possible risk of occlusion of the great vein of Galen as a result of elevation of the tentorium by subtentorial tumours in man.

The presence of Indian ink over the entire cerebral cortex need not be regarded as providing evidence against this view. The highest cerebrospinal fluid pressure encountered in these experiments was 450 mm. of normal saline. Although abnormally high, this pressure is probably far below the maximum, and it is reasonable to presume that a considerable proportion of the cerebrospinal fluid was still being absorbed. It is not surprising, therefore, that the ink was able to spread

over the entire cortex in all these experiments. A careful comparison of brains containing tumours with normal brains failed, however, to demonstrate any pronounced elevation of the tentorium. It is, therefore, very doubtful whether the resulting displacement of the cerebral hemispheres would be sufficient to cause any interference with the circulation of the cerebrospinal fluid over the cortex.

On the other hand, it is evident from Fig. 1 that the tumour is tending to displace the cerebellum in a forward direction. This may be accompanied by a displacement of the brain stem and of the cerebral hemispheres in the same direction, which may ultimately lead to an embarrassment of the circulation of the cerebrospinal fluid over the cerebral cortex. Here again, however, it is doubtful whether the hemispheres are displaced to a significant extent. Moreover, experiments on the effect of artificial supratentorial tumours which are now in progress, would seem to provide evidence that the cerebral hemispheres may be displaced to a considerable degree without having any effect on the pressure of the cerebrospinal fluid in the cisterna magna. It is, therefore, very doubtful whether the raised pressure of the cerebrospinal fluid in the experiments under consideration can be accounted for on such a basis.

(*c*) The venous pressure in the torcular was within normal limits in every case of subtentorial tumour which was uncomplicated by venous clotting. Experimental evidence [5, 6] has also been provided that a raised venous pressure in the torcular is compatible with a normal cerebrospinal fluid pressure. It is improbable, therefore, that the raised pressure of the cerebrospinal fluid can be accounted for on this basis.

To sum up, it would appear that the raised pressure of the cerebrospinal fluid in these experiments may have been caused in two possible ways :—

(1) The tumour may have caused an increased production of cerebrospinal fluid in some way still undetermined. The excess of fluid may have been so great that the absorption apparatus was unable to deal with it, or the normal cerebrospinal fluid channels distal to the cisterna magna may have been relatively too small to permit it to circulate freely.

(2) The circulation of the cerebrospinal fluid may have been obstructed at some point between the cisterna magna and the base of the brain. The obstruction was probably incomplete or intermittent in character.

Considerable improvement, however, will be necessary in the means

available for investigating the circulation of the cerebrospinal fluid before it is possible to decide with any confidence which view is the correct one.

It is necessary, before concluding, to consider the four cases of hydrocephalus. The experimental findings have already been described in detail. Latent hydrocephalus has been encountered in less than one per cent. of laboratory dogs. The condition was symptomless and was discovered during routine examination. It is, therefore, conceivable, although improbable, that the hydrocephalus was present before the tumours were introduced. Experimental tumours probably produce their maximum effect shortly after introduction. After six days, however, the brain may have accommodated itself partially to the tumour, and local œdema, if present, may have had time to subside. It is conceivable, for example, that an obstruction to the circulation of the cerebrospinal fluid which was complete during the early part of the experiment, would later become partial or intermittent. The pressure of the cerebrospinal fluid may then be no greater than that in cases uncomplicated by hydrocephalus. It is impossible, however, in the absence of essential data, to be certain of the precise origin of the hydrocephalus. Nevertheless, the slight but unmistakable dilatation of the aqueduct and of the fourth ventricle which was present in each case, would seem to suggest that the hydrocephalus had not been caused by a temporary occlusion of these structures.

Summary.

(1) The available literature relating to the origin of the increased pressure of the cerebrospinal fluid associated with intracranial tumours is reviewed.

(2) A method is described by which artificial subtentorial tumours, consisting of cotton wool impregnated with paraffin wax, can be produced in dogs and their effects on the intracranial pressures studied.

(3) Subtentorial tumours were successfully produced in twenty-one dogs. The tumours, with one exception, were extradural in situation. The animals were allowed to survive, on the average, for six days. During the survival period they maintained good health and were symptomless. When examined at the end of this period, the pressure of the cerebrospinal fluid in the cisterna magna was found to be raised. The venous pressure in the torcular and the arterial pressure in the femoral artery were within normal limits.

(4) Hydrocephalus was encountered in four of the animals. The

dilatation was moderate in degree, and involved the lateral and third ventricles, although the aqueduct and the fourth ventricle presented definite evidence of slight dilatation.

(5) Indian ink introduced into the cisterna magna spread over the entire cerebral hemispheres in all animals investigated in this way.

(6) A criticism is presented of the method of investigating the circulation of the cerebrospinal fluid by introducing Indian ink into the cisterna magna.

(7) The possible means by which the tumours may have raised the pressure of the cerebrospinal fluid are discussed.

(8) It is concluded that the experimental findings are compatible with the following mechanisms:—

(*a*) There may have been an increased production of cerebrospinal fluid by the choroid plexuses which was brought about by a mechanism still undetermined. The absorption apparatus may have been unable to deal with the excess of fluid, or the cerebrospinal fluid channels distal to the cisterna magna may have been relatively too small to permit it to circulate freely.

(*b*) Displacement of the brain stem may have led to an obstruction of the circulation of the cerebrospinal fluid at some point between the cisterna magna and the base of the brain. The obstruction was probably incomplete or intermittent in character.

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OBSERVATIONS ON THE ROENTGEN TREATMENT OF INTRACRANIAL GLIOMATA WITH ESPECIAL REFERENCE TO THE EFFECTS OF IRRADIATION UPON THE SURROUNDING BRAIN.[1]

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ALTHOUGH in recent years there has been considerable interest in the treatment of the gliomata by roentgen radiation, there remain differences of opinion as to its value and as to the most suitable technique in its application. In the following pages the effects of roentgen rays upon normal nervous tissue will be described at some length—both as recorded in the literature and as seen in tissues examined in connection with the present investigation. Then the effects of irradiation upon the various members of the glioma group will be very briefly considered. Finally, from a consideration of the available data, an attempt will be made to arrive at some temporary conclusions on the subject of the dosage of irradiation to be employed in the treatment of these tumours.

(1) THE EFFECT OF IRRADIATION UPON NORMAL NERVOUS TISSUE.

Historical Survey.

Before roentgen therapy can be used successfully in the treatment of any tumour, it is necessary that the cells of the tumour be more sensitive to the irradiation than the cells of the surrounding normal tissues. The greater this difference in the sensitivity of the tissues, of tumour and host, the more likely is the treatment to be beneficial, since an adequate dose can be administered to the tumour without the production of damage in the surrounding tissue. With a view to determining the sensitivity of the brain tissue to irradiation, numerous experimental observations have been made by various workers. In addition, there are a number of reports of symptoms of nervous involvement following irradiation of the scalp for superficial lesions. The literature dealing with this matter will now be considered, and then the

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results of the examination of a series of brains which had been subjected to intensive irradiation in the treatment of gliomata will be described.

Lyman, Kupalov and Scholz [16] review the literature on the subject of the effect of roentgen rays on the animal brain. They point out that there is disagreement as to the effects produced in young animals, some authors describing definite parenchymal changes, while others are of the opinion that the only alterations are to be found in the vascular system " or other labile elements." In the case of adult animals there is general agreement that little or no direct effect is produced on the nerve-cells and fibres, although changes may be produced in the blood-vessels and a mesodermal reaction called forth. These authors' work consisted firstly in the investigation of the conditioned reflexes in four dogs whose brains had been subjected to irradiation and secondly in the pathological examination of the brains of these animals. Definite physiological disturbance was observed: for example a diminution of spontaneous activity, a disappearance of conditioned reflexes and later the development of signs of diffuse cerebral damage. Pathologically the authors stress the blood-vessel changes and believe these to be the essential features. They noted especially regressive changes in the capillaries, hyaline and sclerotic changes in the arterioles, and an inflammatory reaction around the blood-vessels. Areas of necrosis were present and diffuse degenerative changes, such as fat in the ganglion cells. Demel [10] confirmed the physiological findings of Brunner and Schwartz [5] by the irradiation of four-day old puppies and produced deficient growth, ataxia and retinal changes, together with small hydrocephalic brains. He quotes Brunner as having found changes in the histologically labile elements, acute hyperemia of the leptomeninges, hæmorrhages and œdema, but no changes in the adult ganglion cells, nerve fibres or glia. Scholz [20, 21] reviews previous work and states that young animals react to high doses of irradiation by cramps, ataxia, paralyses or even death, and that the brain shows hæmorrhages. He points out, however, that adult animals can withstand very high doses, the brain simply showing degenerative changes and proliferative alterations in the blood-vessels. In his own dogs, ataxia, paralyses and stupor occurred in those allowed to survive for a period of twelve months after irradiation. On the other hand, animals killed five weeks after irradiation showed no physiological disturbance. In the latter group the pathological changes noted consisted of lymphocytic infiltration around the smaller blood-vessels in the white matter, together with fibroblastic proliferation. There was some swelling of the astrocytes and occasional rod-cells were

seen. The nerve cells were unchanged. The animals killed at a later period showed circumscribed hæmorrhages which the author suggested might be due to capillary injury. The larger blood-vessels showed fibrosis of the adventitia and hyaline transformation in this layer. These latter changes appeared to spread into the surrounding parenchyma. There were no primary changes in the parenchyma, such alterations as were seen in the animals killed after five weeks having disappeared. He notes that none of these changes was found in control animals which had been subjected to similar periods of anæsthesia but had, of course, received no irradiation.

The effect of roentgen irradiation on the production of cerebrospinal fluid is also of interest. In a recent paper which is in accord with the present views on the subject, Skefer [22] states that while small doses diminish the production of cerebrospinal fluid, larger ones at first stimulate its production, but later depress this further. This is of interest in that it suggests that roentgen irradiation may produce a temporary improvement in symptoms in the case of radio-resistant tumours, and thus the therapeutic test is valueless and dangerous.

The observations dealing with the effects of roentgen radiation on the human brain are less numerous. Alpers and Pancoast [1] describe the results of the histological examination of a number of brains which had been subjected to irradiation. The blocks of tissue examined in their cases had been "in close approximation to the tumour" and "under the decompression or bone-flap" through which many of the rays had been directed. The authors observed in these regions a loss of some cortical nerve-cells with an accumulation of fat in others, and also in the capillary endothelium and astrocytes. Since fat appears in the cortical nerve-cells under various conditions, its presence is not attributed to the irradiation, except in the case of the cerebellar Purkinje cells, where none can normally be demonstrated. From a consideration of their findings, the authors believe that much larger doses than hitherto employed by them may in future be used with advantage. It may here be mentioned that such degenerative changes as those described above which occur *in the immediate neighbourhood of the tumour* or *at the site of herniation of the brain through an opening in the skull* may be due, not to the irradiation, but to the tumour itself or the trauma from the margins of the bony defect.

Apart from this work of Alpers and Pancoast, the reports concerning the effects of roentgen irradiation on the nervous parenchyma deal with certain untoward results which have followed such treatment of the

scalp for some superficial lesion. Fischer and Holfelder [12] describe the case of a man with a canceroid tumour of the temporal region which was treated by roentgen radiation. Seven years later he began to have attacks in which he became restless, felt hot and was unable to speak, together with numbness and twitching of the left hand and foot. An exploration was carried out in the right fronto-parietal region. The brain was described as being blue and full. There was no evidence of metastasis. A biopsy revealed a localized amyloid change only, and it is suggested that this may have been the result of the irradiation.

Markiewicz [17] records a case in which five years after the first, and one and a half years after the second, of two roentgen irradiations, for a scalp lesion, a man aged 34 became blind and paraplegic and commenced to have epileptic attacks. Later he developed a roentgen ulcer in the occipital region and died after two years of symptoms. Examination of the brain revealed multiple hæmorrhagic necrotic areas, mostly in the cortex and especially in the occipito-parietal region. There were also changes in the cortical and pial vessels, and the author considers that these were primary and gave rise to the parenchymal degeneration. Colloidal masses were found to be widely distributed through the parenchyma. It will be noticed that these changes resemble those which Scholz [20, 21] described as occurring in the irradiated brains of dogs and which have been described above. Lorey and Schaltenbrand [14] record two cases in which it appears that damage to the nervous parenchyma had been caused by roentgen irradiation for scalp lesions. The first of these was that of a 5-year-old girl who was suffering from trichophytosis of the scalp. Treatment by irradiation resulted in complete epilation within a period of three weeks. Three months after this, hair appeared again on the left side of the scalp, but not on the right. One year after the treatment there began to occur epileptic attacks and left-sided weakness was noticed. One year later the child had an acute episode with fever, convulsions and a left hemiparesis. At the age of 12 (seven years after the treatment) the left side of the body was under-developed and, though major attacks were less frequent, there were numerous minor ones. Roentgen examination of the skull revealed changes which appeared to correspond fairly accurately with the atrophic and telangiectatic changes in the right side of the scalp. A well-marked atrophy of the skull and a superficial calcification within the cranial cavity were present. Encephalography revealed that the right lateral ventricle was wider than the left, suggesting an atrophy of

the right hemisphere. Because of the correspondence of the skull changes and the roentgen-injured region of the scalp with the neurological disturbance, the authors suggested that the irradiation had injured the scalp, cranium and meninges. It was believed that a dural hematoma had developed in this area. This had injured the cortex and given rise to under-development, epilepsy, and a spastic hemiparesis of the opposite side. Finally the inflammatory products in the meninges had become calcified. In a second paper, Schaltenbrand [24] states that the presumptions in the above case were verified by trephination, a pachymeningitis hæmorrhagica being disclosed. He then describes another somewhat similar case, that of a 21-year-old woman who had received roentgen therapy for a microsporonic infection of the scalp when 9 years of age. During the period of this treatment there had been pyrexia on two occasions, associated with which were some signs of bronchitis. At 15 years of age, after it had been obvious for some time that the child was nervous and emotional, she was brought to the clinic because of delirium, associated with fever. She was found to have an aphasia, deviation of her head and eyes to the left and a right flaccid hemiparesis. There were clonic twitchings of the right arm and face. Gradually her mental state improved, the aphasia and hemiparesis disappeared and the attacks of twitching of the right face and arm became less frequent. Encephalography showed a symmetrical ventricular dilatation. At the age of 21 the patient returned with an increase in the frequency of the epileptic attacks. Most of the hair of the scalp was absent and its skin thin and atrophic. X-ray showed patchy defects in the cranium and in one place some flaky intracranial calcification. The author concludes that the original treatment at the age of 9 injured the cranium and brain and that after a latent period of three years an encephalitis-like illness resulted which gave rise to the right hemiparesis and epileptic attacks.

Summarizing, it will be inferred from these observations that there is both clinical and pathological evidence that roentgen irradiation may produce damage in the tissues of the central nervous system. The histological effects have for the most part been considered secondary to the vascular damage which is the direct result of the irradiation. The nervous parenchyma itself has been considered to be relatively resistent.

Personal Observations.

For the present work, six brains were subjected to the histological examination to be described below. The first, used as a control of our

methods, was that of a subject, aged 36, and not afflicted with a brain tumour, who died suddenly while undergoing treatment for a hæmatemesis from a peptic ulcer. Another was that of an older man who died from a brain tumour before any treatment could be given. This brain was examined so that changes produced by the tumour itself might not be wrongly attributed to irradiation in the other brains. The remaining four were the brains of tumour cases which had received large doses of irradiation. In all these cases, blocks of tissue were taken from both the right and left cerebral hemispheres in each of the following regions: (1) Centrum semiovale; (2) prefontal region; (3) striate (occipital) region; (4) temporal region; (5) parietal region; (6) precentral region; and (7) basal ganglia. In addition a block of cerebellar hemisphere was examined in each instance. Each of these blocks was then examined by the following technical methods— Nissl's toluidin blue, Bielschowsky's nerve-fibre method, Cajal's gold-sublimate method for astrocytes, Herxheimer's stain for fat, and Kultschitsky's modification of Weigert's method for myelin sheaths. In a number of instances, Penfield's modification of the Hortega technique for oliogdendroglia and microglia has been used, as also the Van Gieson stain for clearer demonstration of the blood-vessels. The cases will now be considered in detail:—

Case 1.—R. G., Unit No. 141072. Control brain removed from a man, aged 36. In this case it will be of no interest to discuss the clinical history, except to state that the patient died suddenly when responding well to treatment ten days after a large hæmatemesis from a duodenal ulcer. Necropsy was performed six hours post mortem. The histological examination revealed absolutely no abnormality. It is noteworthy, however, that on staining the tissue by Herxheimer's method for lipoid substances, it was found that in a few of the larger cortical neurones there were granules which stained a faint pink, while a few macrophages on the walls of the smaller cortical capillaries reacted in similar fashion. Repeated efforts failed to demonstrate more than this minimal quantity of lipoidal material.

Case 2.—C. Z., aged 51, Unit No. 151482, was admitted to the Billings Hospital, May 15, 1936, complaining of diplopia, headaches, dizziness and mental confusion.

History.—Six weeks previously his illness had commenced with severe frontal headache, more marked on the right side. Shortly afterwards he noted mental confusion and became awkward in using his left hand. Two weeks before admission he began to suffer from dizziness and diplopia.

Examination revealed a somewhat inattentive and confused patient. No papillœdema was present. There was a complete left homonymous hemianopia. The right palpebral fissure was narrower than the left and there was some

weakness of convergence. The other cranial nerves were not involved and motor power and co-ordination were apparently not disturbed. Examination of sensation demonstrated only a deficiency in position sense in the left great toe and left fingers. The abdominal reflexes were somewhat diminished on the left. In walking it was noted that the patient dragged his left toes and did not swing his left arm. Laboratory examinations, including serology, were negative. The pineal shadow was demonstrated by X-ray to be slightly displaced to the left.

A diagnosis of right temporo-parietal glioblastoma was made and on May 23 a right temporo-parietal osteoplastic craniotomy was performed under general anasthesia by Dr. Bailey. No tumour was visible on the surface of the brain, but with an exploratory needle a mass was palpated 3 cm. beneath the surface in the upper temporal region. Owing to a sudden fall in blood-pressure and the fact that it was obvious that the tumour could not be excised, it was decided to leave the operation as a decompression preliminary to irradiation. The patient's condition was poor after operation, and he died two days later.

At the necropsy, which was performed two hours after death, a large tumour was disclosed in the right occipito-parietal region. It extended laterally to within 5 mm. of the cortex, posteriorly to within 3 cm. of the occipital pole and anteriorly as far as the postcentral gyrus. On its cut surface numerous yellow, hæmorrhagic and cystic areas were to be seen. Microscopically the tumour had the typical structure of a glioblastoma multiforme.

The examination of the brain for lipochrome pigment revealed that more of this was present than in the previous case, an occurrence to be expected in view of the difference in the age of the patients. The pigment occurred especially in the ganglion cells, where it took the form of fine granules, and in macrophages gathered around cortical and subcortical blood vessels in which it formed coarser granules. No pigment could be demonstrated in the neuroglia of the cortex or white substance. It was noteworthy that the nerve-cells which contained the pigment appeared in all other respects to be normal, there being no displacement of the nucleus or change in the cell-body or its processes. The change was most marked in the temporal cortex on both sides. The nerve-fibre stains revealed no abnormality in the cells or their processes and no abnormality was detected in the astrocytes or myelin-sheaths (except, of course, in the immediate neighbourhood of the tumour where the astrocytes were swollen and their processes broken up, while the myelin sheaths lying between the tumour cells were fragmented). With the Nissl stain, it was found that the tigroid substance was only faintly stained, due doubtless to formalin fixation, but appeared of normal distribution. It will thus be seen that few changes of significance were produced in the brain around this large tumour. The findings in this brain agree very well with those of Caspar in similar cases which will be discussed later.

Case 3.—P. W., aged 45, Unit No. 80234, a carpenter, was admitted to the Billings Hospital, April 6, 1933, complaining of headaches.

History.—The patient had been subject to sick headaches since childhood, but two months before his admission these had become much more severe, radiating forward from the right occipital region. For a similar period he had become aware of a poor memory, blurred vision, dizziness and numbness of his arms and legs. The visual disturbance had been progressive and more marked in the right eye. The attacks of giddiness had come on especially while walking, surrounding objects appearing to whirl and the patient falling forward. There had been an attack of nausea and vomiting prior to the onset of the other symptoms, but this had not recurred.

Examination.—The patient was mentally slow, but otherwise normal and co-operative. There was tenderness on percussion of the right parietal region of the skull and a resistance to flexion of the neck. Visual acuity was markedly diminished (more so on the right) and both fields, especially the right, were grossly constricted. There was bilateral papilloedema, 4 to 5D on the right and 2 to 3D on the left with small retinal arteries and tortuous veins. There was a slight degree of exophthalmos on the right, and the left pupil was larger than the right, both having normal reactions. There was slight bilateral limitation of lateral gaze and a diplopia on looking to the right. There was also a slight weakness on the left lower face. No abnormality was detected in the motor or sensory system and the reflexes were normal. The gait was a little unsteady but Romberg's sign negative. Laboratory examination, including serology, revealed no abnormality and X-ray of the skull demonstrated no sellar change, pineal shift, or convolutional markings. Ventriculogram on April 13 revealed that the left ventricle was displaced to the left and not filled in its central portion. No filling of the right lateral ventricle was seen.

On April 15 a right frontal osteoplastic craniotomy under ether anæsthesia was performed by Dr. Bailey and revealed an extensive glioma of the right hemisphere with a reddish grey surface-extension in the right frontal region. A portion was removed for histological examination, a decompression made and the wound closed. Histologically the tumour proved to be a cellular glioma, probably to be classified as a protoplasmic astrocytoma, but showing evidences of malignancy in the number of multinucleated cells and the general polymorphism. Following his recovery from operation and between the dates of April 24 and September 12, 1933, he received 12,645 r. units of irradiation (measured in air). The dose was administered through multiple portals. Transitory erythema of the scalp and permanent epilation occurred.

The patient felt well and returned to work. He was seen from time to time and his decompression remained soft until three years later, in March, 1936, when it was noticed at home that he had "lost interest in things." A left hemiparesis gradually appeared and the decompression became tense. He was given 630 r. additional irradiation, but gradually passed into coma on April 24, and died three days later.

A post-mortem examination was performed eleven and a half hours after

death, but the brain had been fixed some hours previously by arterial injection. It revealed flattening of the convolutions of the cerebral hemispheres which was most marked in the right frontal region, this frontal lobe being at least a quarter larger than that of the opposite side. On section the right frontal lobe contained a large tumour mass which extended posteriorly as far as the central region. Histologically the tumour was more cellular and of somewhat more malignant type than that obtained at the biopsy three years previously (Plate XI, fig. 5).

There was a definite and generalized increase in what may be termed lipochrome substance in this brain. It affected not only the nerve cells, but also the walls of the blood-vessels, the macrophages and the neuroglia. The cortical neurones were for the most part uniformly affected and on many occasions the discrete granules of lipochrome pigment, which are seen here normally in later life, had condensed to form a mass which had displaced the nucleus toward the periphery of the cell. In the Purkinje cells of the cerebellum, in which this substance is usually not found, it was abundant and was clearly demonstrable also in the neighbouring basket cells. Around many nuclei, which were obviously those of glia cells in the cortex, there were similar granules of this lipoid material. On the walls of the cortical capillaries the adventitial cells were very frequently seen to be loaded with it (Plate IX, fig. 2) and grouped around the larger cortical and subcortical vessels were macrophages similarly laden. It is to be noted that in the subcortical regions the substance was found only around the blood-vessels, where it was contained in macrophages. The tumour cells also contained this material in large globules.

In the sections impregnated by the Bielschowsky method the changes produced were not as generalized and, excluding those in the right frontal region (the site of the tumour), were most marked and equally so in the temporal cortex of both sides and the left precentral region. In these regions, especially, the nuclei of the nerve cells were eccentric in many cases and the cytoplasm, including that of the apical dendrites, vacuolated with destruction of the neuro-fibrillæ. In Plate IX, fig. 1, is seen a nerve cell, showing these changes. They are no doubt to be associated with the accumulation of excessive amounts of lipochrome substance. In addition to these well-marked changes, it was noted that throughout the brain the neurofibrillæ were not well impregnated. Except in the region infiltrated by tumour, the nerve fibres in the white matter showed no abnormality.

In the Nissl preparations there was noted an almost complete failure to stain the tigroid substance in the cerebral cortical cells, although the technique had been successful in the case of the cerebellar Purkinje cells. Also in both right and left temporal regions and the left prefrontal region (which had shown the most marked changes in the Bielschowsky preparations) well-marked satellitosis and neuronophagia were to be seen in the Nissl specimens. In the preparations to demonstrate astrocytes, the changes were not remarkable. In the temporal regions on both sides there was some clasmatodendrosis and in other regions, where this advanced change was not found, the astrocytes were often found to

have enlarged cell bodies and somewhat irregular processes. In neither Nissl nor van Giesen preparations were any changes demonstrable in the blood-vessels which, therefore, departed from the normal only in having their sheaths infiltrated with the fat-laden macrophages. Except in the region of the tumour, there was no demonstrable change in the myelin sheaths of the nerve-fibres—neither in the tangential nor vertical fibres of the cortex, nor in the subcortex.

To sum up, it may be said that in this brain definite degenerative changes were found. They affected the nerve-cells and, to a less extent, the neuroglia. The blood-vessels were for the most part unaffected. There was no evidence of any mesodermal reaction, though fat-laden macrophages were to be found around most of the small vessels.

Case 4.—E. W., aged 32, Unit No. 77948, unemployed, was admitted to the Billings Hospital on March 26, 1933, complaining of convulsive seizures associated with loss of consciousness which had been occurring for the previous ten weeks.

History.—Two and a half months previously the patient had begun to have attacks in which his arms underwent rhythmical jerking movements, both equally. On one occasion this was associated with loss of consciousness and he believed that he had then remained unconscious for fifteen minutes. Since this attack he had been aware of a constant buzzing noise in his left ear, and at times had noticed a transient unpleasant odour without any obvious cause for it. In addition, throughout the period of his illness his memory had been poor and at times he had had difficulty in naming familiar objects. Since the onset of his other symptoms he had also suffered from a left parietal headache radiating at times to the back of his neck. There had been no vomiting and no visual disturbance. Neither was there any weakness of the limbs, nor sensory disturbance. However, he believed, that his gait had been uncertain.

Examination revealed a well-oriented man who appeared to cerebrate slowly. There was a slight difficulty in expression and in writing certain characters. There was tenderness on percussion of the skull in the left temporo-parietal region and a left hyposmia. Vision was normal as were the ocular fundi, but the visual fields showed a slight defect in the right lower temporal quadrants. The left pupil was slightly larger than the right, and there was a suggestion of hypæsthesia in the area of distribution of the left trigeminal nerve, together with slight weakness of the left masticatory muscles. Further examination of the motor and sensory systems revealed no abnormality and the reflexes were also normal, except that the left abdominal and left cremasteric reflexes appeared to be diminished. The patient's station and gait were undisturbed. Laboratory investigation, including serology, revealed no abnormality and X-ray examination showed a normal skull. A diagnosis of left temporal glioblastoma was made and on March 28, 1933, Dr. Bailey turned down a left temporo-parietal osteoplastic flap and on incision of the cortex in the region of the junction of temporo-parietal and occipital lobes, came upon grey avascular tumour tissue, at a depth of 1 cm. A biopsy was

made, a large decompression left and the wound closed without any attempt at excision of the tumour mass. Histological examination of the tissue revealed that it was a protoplasmic astrocytoma showing some cellular polymorphism and multinucleated cells. It was thought that in addition there might be some participation of oligodendroglia in the growth, though this was not proved by specific impregnation.

Roentgen therapy was commenced immediately and between April 7 and August 18, 1933, 8,178 r. units (measured in air) were administered through multiple portals while between May 29 and July 5, 1934, a dose of 7,250 r. units was given. Thus in a period of just over a year a dose of 15,500 r. had been administered, the first half of this over a four months' period and the second in the much shorter space of six weeks. There resulted a severe dermatitis of the scalp with much weeping. Following this treatment the patient's attacks continued, though at longer intervals, and apart from this he was at first considerably improved. Later, however, he lost his appetite and complained of weakness, listlessness and loss of energy. The decompression remained soft and flat. On April 12 vomiting appeared, together with numbness of the left arm and leg. There was drowsiness, which passed later into coma and the patient died on January 26, 1935. It is of interest to note that at no period did the decompression become tense or bulge.

A necropsy was performed two and three-quarter hours after death and the brain was immediately sectioned, blocks being placed in Zenker's fluid, formalin, formalin-bromide and alcohol. There was found in the left hemisphere a large mass of abnormal tissue extending from the anterior portion of the left temporal lobe to within 2 cm. of the occipital pole. It had one cystic cavity 2 cm. in diameter at its centre and there were numerous surrounding cysts. There was considerable œdema of this hemisphere. Histological examination of several regions in the mass revealed extensive degeneration with some areas of marked astrocytic proliferation—undoubtedly tumour (Plate XI, fig. 6)—and no evidence of malignant transformation.

The results of the examination of the surrounding brain by the various histological methods will now be described. In the material stained by Herxheimer's method, a very large amount of lipochrome substance was demonstrated throughout the brain. This was present in greatest amount in the cortex, where it occupied not only the nerve-cells but was clearly evident in the oligodendroglia and in the astrocytes of the first layer of the cortex beneath the pia mater. A large quantity of the material was deposited in the adventitial cells of the cortical capillaries (as in Plate IX, fig. 2), while in the white matter there were numerous fat-laden macrophages around the blood vessels. The changes were widespread and marked, but on the whole it seemed that there was more of this material demonstrated in the nerve-cells of the right temporal cortex than in those of any other region. In the Bielschowsky preparations, the displacement of the nucleus and vacuolation of the cells with destruction of neuro-fibrillæ, which have above been associated with excess of lipochrome substance, were again clearly seen (as in Plate IX, fig. 1). As was

the case in the Herxheimer preparations, these changes were widespread. It was noticed, however, that the cells in the occipital region of both hemispheres were less affected than elsewhere.

In the Nissl preparations many changes were discovered, and may with benefit be classified into three groups according to whether the nerve-cells, the glia or the vascular tissues are involved. Many of the nerve-cells were found to have heavily stained nuclei and swollen bodies; satellitosis and neuronophagia were widespread. In one small cortical area there was noted an entire absence of nerve-cells and a commencing glial scar (Plate X, fig. 1). The most striking change in the glia was an increase in the cortical, and especially the subcortical astrocytes, many of which were of the swollen type, described above. There were areas in which groups of these large astrocytes were found, the "gliarazen" of German authors. These differ from glial scars in that the nuclei of the astrocytes are separated by cytoplasm and not by a network of fibrils. There were regions in which proliferation of the glia along the blood-vessels was clearly seen—the so-called "glia walls" (Plate X, fig. 4). There appeared to be a proliferation of the microglia, and numerous swollen oligodendroglia were also noted. The changes affecting the vascular system were also numerous. In the white matter there was well marked perivascular infiltration with lymphocytes, plasma cells and macrophages, many of the latter containing the green granules characteristic of altered blood pigment when stained by this method. Numerous small softenings filled with macrophages were encountered (Plate X, fig. 2). Some adventitial thickening of the blood-vessels was also seen and occasional arteriolar-sclerosis.

Specimens prepared by the Cajal gold-sublimate technique demonstrated scattered changes in the astrocytes, but the changes were not uniform and many astrocytes were entirely normal. However, large swollen astrocytes were commonly seen (Plate IX, fig. 7), and in some regions this change had progressed to a breaking up of the processes which had become reduced to aurophilic granules. In Plate IX, fig. 6, a typical example of this clasmatodendrosis is to be seen.

Because of the changes noticed in the microglia and oligodendroglia in the Nissl preparations, sections from the series of blocks were impregnated by Penfield's modification of Hortega's technique for demonstration of these cells. In this way, widely distributed hypertrophied microglial cells were demonstrated. Some took the form of the so-called "rod cells" (Plate IX, fig. 4), while others had become almost amœboid. In the left temporal region many large phagocytes were seen, and it seemed possible that they represented a further change in the hypertrophied microglia, so numerous elsewhere. Swollen oligodendroglia cells (to which little importance is attached) were also conspicuous in these preparations. No changes were observed in the myelin sheaths.

It will be seen that in this brain, which had received larger doses of irradiation than the previous one, much more pronounced degenerative changes were present. These affected not only the nerve-cells, but also the astrocytes,

microglia and possibly oligodendroglia. The blood-vessels were involved to a slight extent only. The clasmatodendrosis and myelin destruction of the temporal lobe might be accounted for by the presence of the tumour, also the proliferative changes in the neuroglia, but certainly not the widespread degenerative changes affecting all parts of the cortex.

Case 5.—J. C., aged 4 years, Unit No. 70249. This example of a medulloblastoma cerebelli will later be briefly considered from the clinical point of view (p. 243). At present the changes found post-mortem in the irradiated brain will be considered.

Specimens prepared by Herxheimer's method revealed a large quantity of lipochrome substance in the cortical nerve-cells and this at an age when there is normally little to be found. In addition, fat in the astrocytes, including those of the first layer of the cortex, was seen and everywhere large microglial cells with their processes laden with fat-granules (Plate IX, fig. 3). In the Bielschowsky preparations there was vacuolation of the nerve-cells with displacement of their nuclei and disappearance of their neurofibrillæ (as in Plate IX, fig. 1). Certain of these cells were seen to be greatly shrunken. The Nissl preparations showed very widespread degeneration of the cortical nerve-cells. Some of these cells were swollen, with their nuclei displaced toward the periphery and the tigroid substance undergoing chromatolysis. Others were shrunken, with nuclei staining very heavily. In addition, in these preparations, large vacuolated neuroglial cells could be discerned as well as numerous large microglia (" rod cells ").

The preparations to demonstrate neuroglia showed widespread swelling of the astrocytes with breaking up of their processes (clasmatodendrosis). The Penfield preparations revealed swollen oligodendroglia, but the numerous large microglia seen in the Nissl preparations were not satisfactorily impregnated. Definite changes in the structure of the vessels themselves were frequently observed. Of these the so-called arteriolar sclerosis was most obvious, with its separation of the intima from the adventitia by a wide hyaline zone. Other vessels showed either intimal proliferation with endothelial cells projecting into the vascular lumen, or an adventitial hypertrophy.

It will thus be seen that widespread changes of a type similar to those already described were present in this brain also. They affected the nerve-cells, neuroglia, microglia and even the blood-vessels. The nerve-cells showed more definite evidence of degenerative changes here than in any other case, no doubt due to the age of the patient.

We have examined also the brain of another child (C. S.), aged 5½ years, Unit No. 89864, who received altogether a dose of 14,229 r. units from September 26, 1933, to May 7, 1934, for a cerebellar medulloblastoma, but who died less than a month after completion of the irradiation. The changes in this brain may be briefly summarized by saying that they resembled those found in the brain of Case 3, the nerve-cells being mainly affected. These were swollen and vacuolated, their nuclei being displaced and heavily stained.

(2) The Effect of Irradiation upon Tumour Tissue.

Bailey, in 1925, suggested that the varying effects of roentgen irradiation upon the gliomata might be due to histological differences within this group of tumours. Following the classification of these tumours by him, it has come to be recognized that the various members of the group differ not only in their gross and microscopical structure, life history and sites of predilection, but also in their response to treatment, whether surgical or radiological. The sensitivity of these different types to roentgen therapy will now be very briefly considered.

Undoubtedly the medulloblastoma is the most sensitive to irradiation of the gliomata. In 1928 Bailey, Sosman and van Dessel [3] reported eleven cases so treated with the average survival period of thirty-nine months, a considerable improvement on the average survival period in non-irradiated cases, which is usually less than twelve months. These authors also pointed out that since the tumour spreads by seeding itself throughout the subarachnoid space, adequate treatment must involve irradiation of the whole central nervous axis. Bailey [2] has described the regressive histological changes occurring in this tumour following roentgen therapy. Other writers have confirmed the above work (e.g. [1, 8]), and many of the cases treated in this clinic have benefited considerably.

As an example may be quoted a boy, aged 4 years (Case 5—above), who was admitted to the Billings Hospital in October, 1932, because of unsteadiness of gait, having had symptoms for six months. A diagnosis of tumour of the vermis was confirmed at operation, when a typical medulloblastoma was disclosed. A biopsy only was carried out. Irradiation caused his symptoms to disappear, and later had the same effect on lumbar pain which appeared in April, 1933, and again in March, 1934. Later, however, irradiation proved unavailing, and the child died in February, 1935. This child had received 13,789 r. units between November 11, 1932, and April 17, 1934. The irradiation in this and the previous cases was delivered at 200 k.v. and 25 m.a.; filtration 1 to 1·25 mm. Cu. plus 1 mm. Al.; intensity about 38 to 42 r. per minute; F.S.D. 50 to 60 cm.; 200 to 300 r. per sitting continuously or in series with varying rest periods. Post-mortem examination revealed that the tumour had spread widely through the subarachnoid space. In Plate XI, figs. 1 and 2, the tumour tissue as it appeared before and after irradiation is seen. Rarefaction has occurred, there is an increase in the collagenous stroma and the nuclei are small and pyknotic in the post-irradiation specimen.

In attempting to assess the sensitivity of the glioblastoma multiforme one is faced with a problem of greater difficulty. The unirradiated tumour so often shows numerous areas of degeneration, hæmorrhage and considerable variations in histological picture in its different parts that it becomes very difficult to attribute any changes observed in irradiated specimens to the irradiation. Thus while some have described structural alterations in this tumour type and believe them to be due to irradiation [1, 9, &c.] the authors feel that the best evidence of its radiosensitivity will be clinical. In the literature no reports of considerable clinical improvement following irradiation of the glioblastoma multiforme have been found and the same holds true for the patients treated in this clinic. An exception, however, will now be described.

S. S., aged 42, Unit No. 91886, unemployed, was admitted to the Billings Hospital on October 13, 1933, complaining of convulsions, right-sided weakness and difficulty in expressing himself.

History.—Four years previously, he awoke one night, felt unaccountably anxious and suddenly became unconscious. He remained so for five minutes. Then he got up and walked around only to become unconscious again, when he returned to bed. The coma persisted for twenty-four hours, during which time he had a number of generalized convulsions. Two and a half years before admission, he began to have convulsions every three to five months. These were right-sided and associated with loss of consciousness, lasting about thirty seconds. There was an aura of stiffness of the right thumb and he believed that he could abort the attacks by hyperextending this thumb. During these two and a half years there had been a progressive increase in weakness of the right limbs, and the patient noticed an increasing difficulty in expressing himself. Headache was rare. No nausea or vomiting was present. There was no visual disturbance.

Examination revealed an intelligent and co-operative patient who had difficulty in naming common objects. There was no tenderness on percussion of the skull and movements of the neck were full and painless. Vision was normal and there was no papillœdema, although the retinal veins were engorged. There was a paresis of the right lower face. The motor system showed a right spastic hemiparesis. There was no sensory disturbance. The tendon reflexes were hyperactive on the right, the abdominal reflexes were absent on this side, but the plantar responses were normal. Examination of station and gait revealed that the patient was unsteady when standing on the right leg and that he did not swing his right arm in walking. Laboratory examinations, including serology, were negative. X-ray revealed a midline pineal shadow and a normal sella turcica.

A diagnosis of tumour in the left central region was made, and on October 24, 1933, a left frontoparietal osteoplastic craniotomy was carried out

by Dr. Bucy under local anæsthesia. A firm area measuring 2 cm. in diameter, with dilated pial vessels overlying it, was palpated in the posterior extremity of the second frontal convolution. Elsewhere the convolutions were slightly flattened. The area of the precentral gyrus for the thumb and fingers was localized immediately posterior to the tumour by faradic stimulation. A biopsy only was performed (because of the site of the tumour), and the tissue was reported by Dr. Bailey to be from a glio-blastoma multiforme. A subtemporal decompression was made and the wound closed.

Post-operatively there was an expressive aphasia which rapidly improved, and on his discharge following roentgen therapy, the patient felt well, complaining only of slight difficulty in speech and a little right-sided weakness. Following a course of therapy in which he received 6,068 r. units between the dates of November 3 and December 20, 1933, through a single portal of diameter 10 cm. situated over the tumour, he lost all symptoms, apart from some slowness of speech. There was a permanent epilation of the irradiated area and a transitory exfoliative dermatitis. Since then he has had no convulsions and his decompression is flat. When last heard from on January 8, 1936, he was in excellent condition; he has since moved to another city and to an unknown address.

This would appear to be an example of a malignant glioma, so situated that any increase in size would be at once reflected in the patient's symptomatology. The tumour reacted so favourably to treatment that the patient remains symptom-free after more than fifty months. We have never had any other experience so encouraging with this type of glioma. It is realized that there are certain features in the case unusual in a glioblastoma. The pre-operative history is long, but this is not uncommon when the first symptom is convulsions. The histological picture also is not entirely characteristic, but the tumour is definitely of malignant type with numerous mitoses and the favourable effect of roentgen-therapy upon it is an encouragement to treat such cases in a thorough manner. In this case the situation of the tumour was such that intensive irradiation could be administered directly over the growth through a decompression.

On theoretical grounds one would not expect gliomata composed of more mature types of cell (e.g. fibrillary astrocytoma and ependymoma) to be influenced by irradiation to any marked extent. In this clinic specimens of pre- and post-irradiation tissue are often indistinguishable. Again, in most cases it is impossible to point to clinical improvement as being the result of irradiation, since the tumours are of slow growth, and the patient may live for many years after a partial excision and decompression, without irradiation. The following case may perhaps

be considered evidence of the resistance of the fibrillary astrocytoma to irradiation.

A child, aged 4 years, was admitted to the Billings Hospital in December 1932, with symptoms and signs which led to a diagnosis of a left-sided cerebellar tumour. Exploration revealed a solid astrocytoma of the left hemisphere, and as the child's general condition was poor no attempt at excision was made, and a biopsy only carried out. Subsequently a dose of Roentgen radiation, totalling 9,154 r., was administered. As a result of recurrence of symptoms the posterior fossa was re-explored in May, 1935, when a huge solid tumour was again encountered. In this case it was hoped that intensive irradiation might bring about the cystic degeneration so common in cerebellar astrocytomata, but no such change occurred, a fact which lends support to the belief that the more mature types of glioma are resistant to the therapy.

In spite of this, there would seem to be a definite indication for following surgical treatment of some of these benign types of glioma with roentgen irradiation. This indication is the knowledge that these tumours may undergo what might be described as malignant degeneration. Globus [13] has reported a series of five cases in which he states this change had occurred, and Müller [18] describes three similar cases. Bailey, Sosman and van Dessel [3] also believe that such a change may occur, especially in protoplasmic astrocytomata and oligodendrogliomata, and for that reason suggest that operative treatment of these should be followed by irradiation. It has often been recorded that a slowly-growing glioma, present for several years and producing few symptoms, grows rapidly after partial excision and decompression, and quickly produces severe symptoms. Moreover, in benign gliomata, undisturbed by operation, foci with a more malignant appearance may sometimes be found. In Plate XI are photomicrographs of tumour tissue. In fig. 3 is seen the structure of the greater part of a tumour mass (a protoplasmic astrocytoma), while in fig. 4 is seen the structure of a small central nodule in which are to be found numerous mitoses and the cells present the arrangement so characteristic of glioblastoma multiforme. This tumour was found at post-mortem in the frontal lobe of the brain of a man (W. M.), aged 27, who had a history of headaches and failing memory for four months and who died before any treatment could be given him. This young man had long had behaviour difficulties and his academic work had constantly deteriorated to the distress of his father, who had wished him to become a physician. There is every reason to suppose, therefore, that the tumour had been present for some years. It is obvious, of course, that before a tumour can be finally

proved to have undergone this de-differentiation, a thorough examination of a number of blocks taken from its various parts should have been carried out at the time of the original operation. This is usually impossible, and the data will remain inconclusive. It should not be necessary to remark that, should the tumour be completely removed at the first operation, subsequent irradiation cannot be credited with the cure. This seems to have happened in the case of certain hæmangioblastomata reported by Sachs, Ruberstein and Arnisen [19]. These authors definitely state that the tumours were removed, often with considerable surrounding brain. The bed of the tumour was then irradiated and the surprising conclusion is drawn that the hæmangioblastomata are very favourably influenced by irradiation. Thus, since it is believed that evidence is now available to show that the more malignant gliomata can be at least retarded in their growth by roentgen therapy, it would seem rational to irradiate also those types which are believed to undergo malignant transformation; particularly the protoplasmic astrocytoma and oligodendroglioma.

Discussion.

In this paper there has been described a number of changes occurring in brains which were irradiated in the treatment of gliomata. The possibility of these changes being of post-mortem origin may be immediately dismissed. The longest interval between death and the removal of the brain was fifteen hours. Most pathological studies on the Continent are done on brains which are at least twenty-four hours post mortem, since they cannot be removed earlier. The changes such as we describe are not found in such brains. Some of our material was obtained within three hours after death and immediately fixed in optimal fixatives. But before concluding that these changes are the result of the irradiation, it is important that those which may result from the presence of gliomata should be clearly distinguished. Stern [23] has described at length the changes which may be found in brains which harbour tumours. In connection with the nerve-cells, he remarks that no severe "cell sickness" is ever seen. "Chronic cell change" is not infrequent, and he also records that there is frequently an absence of intracellular neurofibrillæ, though these are clearly demonstrable in the dendritic processes. Rarely is any pathological amount of fat demonstrable in the ganglion cells or in the adventitial sheaths of the blood-vessels. As regards the glia, apart from gliosis immediately around the tumour, no remarkable changes are seen; this being especially true of

the glia in the cortex. This author believes that there is sometimes an overgrowth of fibrillary neuroglia, and quotes Alzheimer's finding of amœboid glia in the immediate neighbourhood of a tumour. There is never any perivascular infiltration with plasma cells and lymphocytes and the increase in the number of blood-vessels recorded by Reichert was not found. Such high grade changes as diminution in the number of tangential medullated fibres in the cortex, reported by Raymond and others, were never found, except in the brain hernia through a palliative trephination. The author concludes his review by stating that there is great variation in the picture from case to case, and in many instances no change whatever is to be found. The work of Caspar [7] (confirmed by Biondi [4]) dealing with the same subject may now be briefly reviewed. He states that grossly there is always swelling of the brain around a tumour. This, in some cases, is so extensive as to involve an entire hemisphere. The most characteristic histological change is a rarefaction of the brain tissue which involves especially the white matter and the first layer of the cortex, so that these may have a loose and almost lace-like texture. There is a widespread dilatation of surrounding blood-vessels, which he regards as the cause of the swelling, and in some cases a capillary fibrosis. The nerve-cells themselves show little change, though there may be some falling out of those in the third layer of the cortex, together with an increase in satellitosis. Turning to a consideration of the glia, Caspar notes that there is no change in the white matter, but in the cortex there are found swelling of the astrocytes and clasmatodendrosis. While there is no hyperplasia of these elements, there appears to be an increase in the fibres in the first layer of the cortex and in the subependymal region. He stresses particularly the fact that in undifferentiated gliomas there is complete absence of any reactive change in the surrounding glia. The same is true for the brain in relation to extra-cerebral tumours (e.g. meningiomas), and the author believes that when proliferation of glia is seen at the margin of one of the more differentiated gliomata the apparent change is a part of the tumour, not a reaction to its presence. He finds no change in the oligodendroglia and microglia, and there is rarely any accumulation of macrophages at the margin of the tumour. These various changes are for the most part seen close to the tumour, but in some cases extended for several centrimetres beyond its immediate neighbourhood. Their presence at once makes it obvious that in deciding whether or not roentgen radiation has produced changes in the brain tissue, it is necessary to examine tissue which lies at a considerable distance from the tumour. The

findings in our Case 2 above agree in general with those of Caspar. In our experience, proliferative changes in the neuroglia may be widespread in brains harbouring astrocytomas and in the oligodendroglia of brains harbouring oligodendrogliomas, but no general changes occur with glioblastoma multiforme or medulloblastoma.

The changes described in the irradiated brains examined in connection with this work were controlled against both a brain which did not contain a tumour and one which did, but in which the patient had received no treatment by roentgen irradiation. No changes in any way comparable with those found in the irradiated brains were demonstrated in these two cases, and none of similar type has been described in the literature. As further evidence that the changes described in the irradiated brains had been produced by the irradiation, it may be pointed out that of the first two of these (Cases 3 and 4) both had large tumours which had compressed the surrounding brain over a relatively long period. Yet, as has been described, by far the most marked histological changes were found in the brain which had harboured the tumour for the shorter time, but which had received a considerably heavier dosage of irradiation. Again, in the cases of the two examples of medulloblastoma described above, in which one brain showed gross and the other relatively slight changes, after both had been subjected to heavy doses of irradiation, the case showing the greater changes had lived nearly a year after the completion of the irradiation, whereas the other child died within a month. Other clinical observations, for example those of Schaltenbrand, indicate that the time which has elapsed after the irradiation may be an important factor in the production of degenerative changes. Individual variations of sensitivity to irradiation must also play a role as with other tissues. The alterations observed may now be reviewed. None which could be definitely attributed to the irradiation were noted in the leptomeninges. Such appearances as thickening and fibrosis were often demonstrable, but would seem to be explained by the healing of areas traumatized at operation. In the cerebral cortex, and to a less extent in that of the cerebellum, structural alterations were numerous. The nerve-cells showed various retrogressive changes. In many the cell body was swollen and rounded, with the nucleus displaced towards the periphery. Examination of these cells by suitable methods revealed a great excess of lipochrome pigment, often aggregated into large masses, and this material appeared to displace and even destroy the neurofibrillæ. Other nerve-cells were shrunken with darkly staining nuclei, and cytoplasm and irregular processes. No

abnormality could be made out in either myelinated or non-myelinated nerve-fibres, except when they were obviously directly involved in the tumour growth. These changes varied from case to case, being mild in one (Case 3), extremely marked in others (Cases 4 and 5), and in general, most severe in the cases which had received the heaviest dosage provided a sufficient time had elapsed after irradiation.

Turning to the interstitial tissues of the cortex, it was noted that the protoplasmic astrocytes impregnated more easily than normally and were often hypertrophied, while the fibrillary astrocytes (in the first layer and immediate subcortical region) were often greatly hypertrophied with swollen bodies. In some areas clasmatodendrosis was well marked. The presence of lipochrome substance in these cells was also frequently observed. Swelling of the oligodendroglia and lipochrome substance within these cells was common, as was marked hypertrophy of the microglia with the formation of rod cells and even perhaps macrophages. Many of the microglial cells contained quantities of lipochrome pigment, and their numbers appeared increased. In the cortical capillaries the adventitial cells were often found to be loaded with lipochrome substance. Surrounding the large blood-vessels were numbers of macrophages containing this substance. These cells gave the impression of being in the process of migration from the surrounding tissues to the blood-vessels. In the cortex in one Case (4) there were found areas of glial scar-formation with an absence of nerve-cells and also small areas of necrosis filled with macrophages.

In the white matter of the hemispheres, no abnormality was observed in the nerve-fibres, but the interstitial tissues showed changes similar to those outlined above. Of these, the changes in the astrocytes were often marked and evidence of glial overgrowth was seen in the "glia walls" and "cytoplasmic glia" above described. In one brain well-marked changes in the vascular system were observed in both cortex and medulla. Perivascular lymphocytic infiltration, arteriolar hypertrophy, with hyalinization of the media and swelling of the intimal coat, and vast numbers of macrophages full of lipochrome pigment in the walls of and gathered around the vessels, were all seen. However, it should be pointed out that in the remaining cases no vascular reaction other than slight medial thickening was seen and it therefore seems certain that in none was the vascular change primary or the factor responsible for the alterations in the nervous tissue itself. This is especially important in the case of medulloblastomata. Here in the terminal stages the lepto-meninges were widely infiltrated and it might be expected that vascular

obstruction would play a rôle in the production of degenerative changes in the nervous parenchyma. But we have made examination of non-irradiated cases (not herein reported) and no such changes are found in them.

The evidence that roentgen irradiation can injure the normal nervous tissues when administered in therapeutic doses is, however, not entirely histological. Cases from the literature have been quoted above in which, in both man and the lower animals, physiological disturbances have followed irradiation. In some of the human cases, it would seem that the disturbance has been brought about by a considerably smaller dosage of irradiation than is often employed in the treatment of the gliomata. In the patients of this series who were treated by irradiation the clinical evidence of resulting intracranial disturbance was of two types. In the first place, there frequently occurred the well recognized immediate reaction to the therapy which is characterized by drowsiness and even coma, with vomiting, and diminished pulse and respiration rates. This is almost certainly due to a sudden rise in intracranial pressure, which is probably brought about by congestion and œdema in and around the tumour, if not throughout the brain [15]. In the second place, certain of the cases which terminated fatally after roentgen therapy did so without exhibiting the signs of raised intracranial tension which are almost invariably seen as death approaches in cases which have not received such therapy. In these cases the decompression has remained soft and even flat or sunken. Such patients become listless, anorexic and anæmic. They gradually fail and finally die in a cachectic state.

This was the case with R. H., aged 36, Unit No. 84923. A cerebral exploration in the right temporal region was performed in June, 1933, and a soft vascular subcortical glioma found. A biopsy was made and a decompression left over the tumour. The tumour proved microscopically to be glioblastoma multiforme. He received between July and November, 1933, through multiple portals, 4,615 r. Again, from April to July, 1934, he received 2,830 r. The result was complete and permanent epilation of the scalp but only transitory erythema. He was very well and working until January, 1935, when he began to complain of headache and general weakness. Between May and July, 1935, he was given 2,280 r. additional radiation, but he steadily declined and died August 30, 1935. The decompression was never at any time tense although slightly bulging. Necropsy was refused.

It is suggested that in such cases, the roentgen therapy may have been a factor in bringing about a fatal result, although further study

would be necessary before such a statement could be made with assurance. It might be noted here that the child C. S. (p. 242 above), who received a dose of 14,229 r. over the cranium and 6,228 r. over the spinal column in the relatively short period of seven months declined rapidly and died some eight months after his operation, whereas similar children treated more conservatively live thirty-six to forty months on the average.

From an examination of the available evidence, both that presented in the literature and in the investigation carried out in connection with this work, it is considered that roentgen irradiation of intracranial gliomata is a therapeutic method of established value. Although it is generally agreed that the medulloblastoma—one of the most undifferentiated of these tumours—is extremely sensitive to irradiation, nevertheless after several treatments it usually becomes resistant and its growth can no longer be restrained. However, symptoms may be relieved and the fatal issue postponed for a considerable period in certain cases. The histological picture of irradiated medulloblastomata also demonstrates their sensitivity to this treatment.

It is believed that another of the more rapidly growing gliomata, the glioblastoma multiforme, is sensitive to irradiation though less so than the medulloblastoma. The clinical record of what is believed to be one example of this tumour has been briefly presented and seems to indicate a complete arrest of the development of the lesion after more than fifty months. While some have attempted to ascribe to irradiation certain retrogressive histological changes in glioblastomata which have received roentgen therapy, we believe that such descriptions are of doubtful value. The histological features so often differ from one part of the tumour to another that it seems to us difficult, if not impossible, to distinguish between these normal variations and any possible effect of roentgen therapy.

As would be expected from the experience gained in treating other tumours by irradiation, the more rapidly growing types mentioned above are by far the most sensitive. However, there would seem to be good reason for treating in a similar manner other more slowly growing tumours composed of more mature cell types, because some of these have a tendency to undergo malignant transformation and in this condition they would theoretically be sensitive to irradiation. It is therefore believed that in these cases irradiation should be given following partial and even supposedly complete surgical extirpation. Thus, while at the present time roentgen radiation may be regarded as

the main therapeutic agent in the case of medulloblastoma and glioblastoma multiforme, it is at the same time to be regarded as being an important accessory to surgery in the treatment of some other more slow-developing gliomata, notably the protoplasmic astrocytomata and the oligodendrogliomata.

There are some (Cutler, Sosman and Vaughan [8]), who consider that in certain cases roentgen treatment should replace surgery, especially in the medulloblastomata, since lasting result cannot be accomplished by the latter. We believe, however, that in every case an exploration should precede irradiation, and this for two reasons. In the first place, it is not possible to make with certainty an accurate diagnosis of the tumour type. By irradiating a lesion such as a cystic astrocytoma of the cerebellum, which is very amenable to surgical treatment, valuable time will be lost and irreparable damage may develop, even if the lesion be later successfully treated surgically. Some believe that irradiation might be regarded as a therapeutic test for medulloblastoma, but cases have been described in which temporary improvement has followed similar treatment of cerebellar astrocytomata, and very serious diagnostic errors are likely to be made if such a belief becomes general. Such temporary improvement is indeed to be expected if irradiation diminishes the secretion of cerebrospinal fluid [22]. In the second place it is considered that surgery should always precede irradiation, since it allows of a decompression being made and thus reduces the dangers of the reaction which so frequently follows irradiation and which is presumably due to swelling of the tumour and its surroundings with a resulting rapid rise in intracranial pressure.

The question of technique and dosage of radiation will now be discussed. Irradiation therapy rests upon an empirical basis because practically nothing is known of the mechanism of action of X-rays and gamma rays upon living protoplasm, or why malignant neoplastic cells are frequently more profoundly influenced than normal cells. Clinical experience furnishes the only guide at present for the mode of administration of irradiation in the treatment of neoplasms. In the case of cutaneous carcinomas large doses varying from 5,000 to 6,000 r. will destroy practically all basal-celled carcinomata of small or moderate size, and will also sterilize the majority of small squamous-celled growths. In squamous-celled carcinomas of the nasopharynx, tonsils and larynx, a tumour-dose of approximately 4,500 r. appears to afford the optimum opportunity for destruction, and clinical experience would indicate that approximately 20 to 25 per cent. of such cases may be controlled locally for five years or more.

There is little more than these positive observations to afford a basis upon which to develop a technique for the irradiation of intracranial neoplasms, and indeed experience with radio-resistant epithelial tumours (colon, stomach, &c.) would indicate that these observations might not at all be applicable to brain tumours.

Tissue Tolerance.

The optimum method for irradiation of neoplasms would seem to be the administration of the optimum dose with minimum reaction in the surrounding normal tissues. Clinical experience has shown that where excessive doses have been administered, resulting in serious damage to the normal tissue, the neoplasm is not controlled. The optimum dose for the destruction of the neoplasm would appear to be a dose that is less than the minimal one for permanent damage to the normal tissues. The margin between these two doses may well be a very narrow one. Thus the maximum normal tissue-tolerance-dose would represent a point beyond which irradiation is futile and harmful. From the cases cited above, it would appear that large doses of the magnitude of 15,000 r., even though administered during a series of treatments extending over several months, are excessive, and eventually induce irreparable damage in the brain without destroying or permanently controlling the growth of the glioma.

Optimum Dose.

Whether the optimum tumour-dose of 4,500 r. which appears to obtain for nasopharyngeal squamous-celled carcinomata also holds for intracranial tumours is a question that can be ascertained only by further clinical observations. The best result obtained in the small series reported above was in the case treated in a manner somewhat similar to that employed in naso-pharyngeal carcinomas. This dose may be delivered to cerebral tumours which are not too deeply situated, by making use of a single portal situated directly over the tumour. This portal should not exceed an area of 100 sq. cm. and daily doses of 150 r. may be given for forty days. Two opposing portals, but of smaller size (8 by 8 or 6 by 6), may also be employed, administering 3,000 r. to each over a similar total period. In deeply situated neoplasms three or more portals may be necessary to obtain a tumour-dose approximating 4,000 to 4,500 r.

In the case of the medullablastoma, which is highly sensitive to irradiation in that there is immediate and rapid regression, the problem of irradiation therapy may be quite similar to that in lymphoblastoma,

where there is immediate response, but an ultimate high degree of radio-resistance. Limited experience would indicate that the optimum tumour-dose, not for cure, which may be impossible, but for prolonged control of the neoplasm, is somewhat less than 4,500 r. In Hodgkin's nodes for example, the tissue effects produced by 700 r. in one case and 3,000 r. in another case, were found to be identical.

It is, of course, frequently impossible to administer such large doses. Irradiation therapy once begun must be discontinued in many instances after relatively few treatments because of the general depression and the poor condition of the patient. However, in planning courses of therapy, the tumour-dose of 4,000 to 4,500 r. may be envisaged as a goal to be obtained if at all possible.

Time Factor.

The time-factor is of prime importance in the irradiation therapy of tumours, because wide variations in tissue reactions are produced when a given large dose is administered in one sitting, divided between several succeeding sittings or fractionated in short series, alternating with periods of rest. The principal reason for this is the factor of cell-recovery from the effects of irradiation. Obviously a quantity of irradiation, if delivered in a short period, may produce normal tissue-damage resulting in a failure of the treatment, while the same dose administered in proper chronology may affect the destruction of the neoplasm. There is still a question as to the proper time-factor for the treatment of naso-pharyngeal carcinomas, where numerous observations have been made. In the case of intracranial neoplasms, observations have been too few to permit of definite conceptions of what may be the proper time-factors. The question is further complicated in the case of brain neoplasms by the fact that the magnitude of normal tissue-reactions in the brain might produce general symptoms warranting cessation of treatment, whereas similar reactions in less vital regions are relatively well tolerated. Limited experience, however, would indicate that five or six weeks is a safe period in which to administer approximately 5,000 to 6,000 r. surface dose to one cranial portal of the size indicated.

Another point upon which there is still debate, is the importance of the intensity with which the irradiation is administered. It has been repeatedly shown that higher intensities produce more profound vascular reactions in the skin [22]. If this holds for the deeper structures as well, irradiation should be administered to the brain in intensities not

exceeding 10 r. per minute, in order to avoid as much as possible unduly severe vascular reactions. For this same reason we feel that the administration of large doses in one sitting during the operation, while the bone flap is reflected (as recently recommended in some clinics [11]) is contrary to good judgment, and will not accomplish the desired results.

Limitations of the Irradiation Therapy of Gliomata.

It is generally agreed that irradiation is most effective in neoplasms of anaplastic cell-type and least effective where the cells are quite mature. In the present state of knowledge and experience in the irradiation therapy of the gliomata it would seem predictable from the cell-type, that a large percentage would fall into the category of those neoplasms which cannot be destroyed by present forms of irradiation. Restraint of growth may however be possible in an increasing number of cases as further experience is gained with various techniques.

Conclusions.

(1) Roentgen irradiation is capable of giving rise to degenerative changes in the tissues of the central nervous system. These changes involve not only the nerve-cells, but also the neuroglia and blood-vessels.

(2) The alterations in vascular structure do not appear to be responsible for the production of the parenchymal changes. Both are the result of irradiation.

(3) Roentgen therapy, preceded by accurate pathological diagnosis and a decompression, is of value in the treatment of the gliomata. Medulloblastoma, and to a less extent, glioblastoma multiforme, react most favourably to this treatment.

(4) Since certain of the more benign gliomata possibly undergo malignant dedifferentiation, surgical treatment of these should be followed by roentgen irradiation in an effort to prevent or retard this change.

(5) In view of the damage to the normal brain which may be produced by large surface doses of irradiation, suggestions are put forward as to what may be a more suitable method of employing roentgen therapy.

One of us (J. E. A. O'C) carried out his part of this work when attached to the service of Dr. Percival Bailey, as a Rockefeller Foundation Fellow, and must express his indebtedness to Dr. Bailey for the opportunity to pursue the investigation, for his advice in connection with the preparation of the histological specimens, and especially for his invaluable assistance in evaluating the changes observed.

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EXPLANATION OF PLATES.

PLATE IX.

FIG. 1.—Degenerating vacuolated pyramidal cell in the left central region. Bielschowsky, × 600. Case 3.

FIG. 2.—Fatty degeneration of adventitial cells of a small cortical blood-vessel in left prefrontal region. Herxheimer, × 300. Case 3.

FIG. 3.—Two microglial cells filled with lipochrome granules. From the left temporal subcortex. Herxheimer's method, × 600. Case 5.

FIG. 4.—Hypertrophied microglial cell from the cortex of the right frontal region (rod-cell). Hortegas silver carbonate, × 600. Case 4.

FIG. 5.—Macrophages gathered around small cortical blood-vessel in the right parieto-occipital region. Nissl, × 300. Case 4.

FIG. 6.—Swollen protoplasmic astrocytes, some undergoing clasmatodendrosis, from the cortex of the right parietal region. Cajal's gold sublimate, × 600. Case 4.

FIG. 7.—Swollen protoplasmic astrocyte from region of the left basal ganglia. Cajal's gold sublimate, × 600. Case 4.

PLATE X.

FIG. 1.—Small patch of ischæmic necrosis from the cortex of the left paracentral lobule. Nissl, × 110. Case 4.

FIG. 2.—Small softening in the cortex of the right middle temporal gyrus. Nissl, × 110. Case 4.

FIG. 3.—Swollen hypertrophied neuroglial cells from the cortex of the left middle temporal gyrus. Nissl, × 430. Case 4.

FIG. 4.—Unusual glia wall formation about blood-vessels in the right frontal cortex. Nissl, × 215. Case 4.

PLATE XI.

FIG. 1.—Case 5.—Tumour removed at operation before roentgen irradiation. Structure that of a typical medulloblastoma. Hematoxylin-eosin, × 150.

FIG. 2.—Case 5. Tumour from cerebellum obtained at necropsy after intensive irradiation. For comparison with previous photograph. Hematoxylin-eosin, × 150.

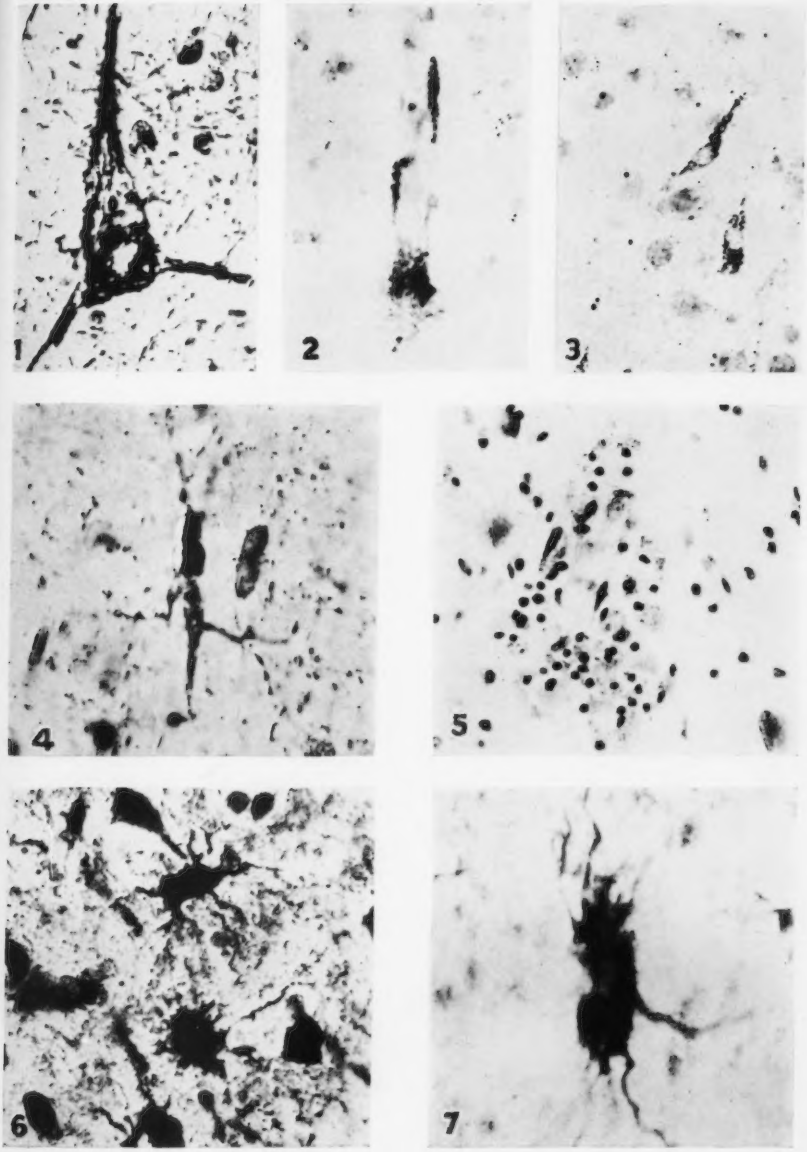
FIG. 3.—Main mass of tumour; case W. M. Structure that of a typical protoplasmic astrocytoma. Hematoxylin-eosin, × 300.

FIG. 4.—Nodule in centre of tumour; case W. M. Focus of increased malignancy. Hematoxylin-eosin, × 300.

FIG. 5.—Tumour from Case 3 at necropsy. Protoplasmic astrocytoma. Hematoxylin-eosin, × 300.

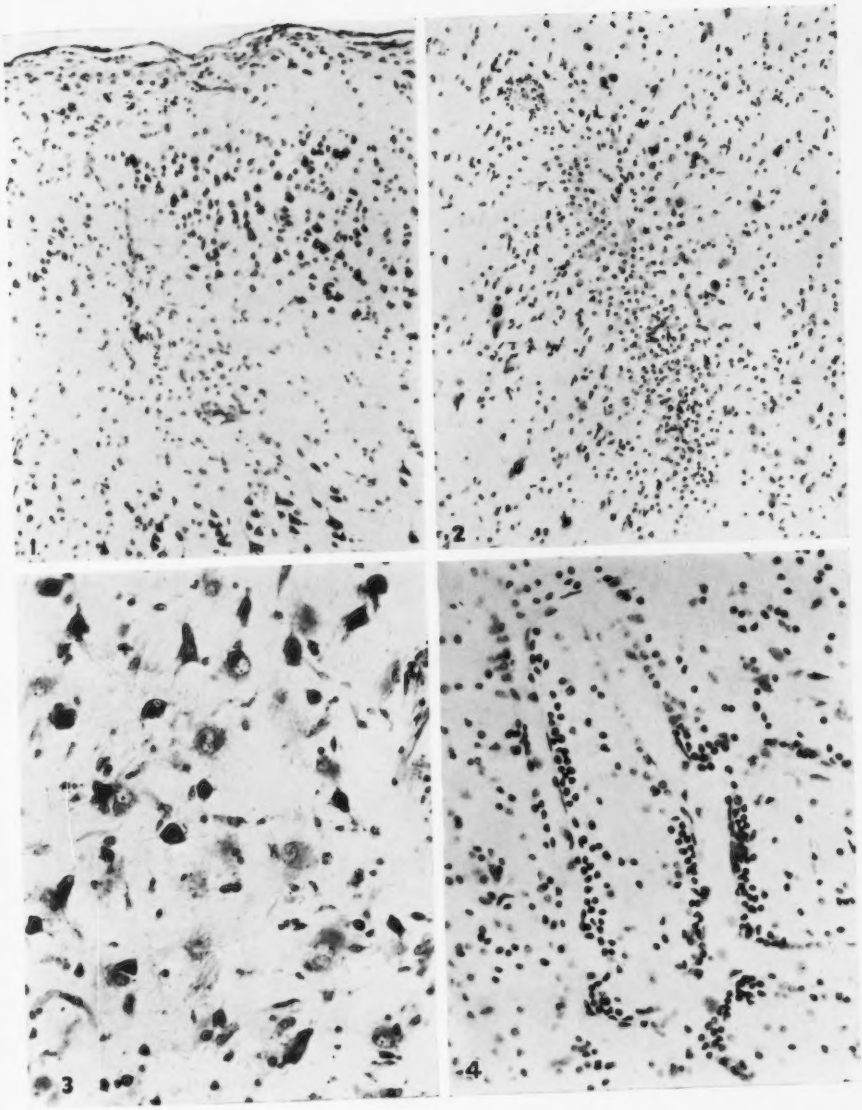
FIG. 6.—Tumour from Case 4 at necropsy. Protoplasmic astrocytoma. Hematoxylin-eosin, × 300.

PLATE IX.



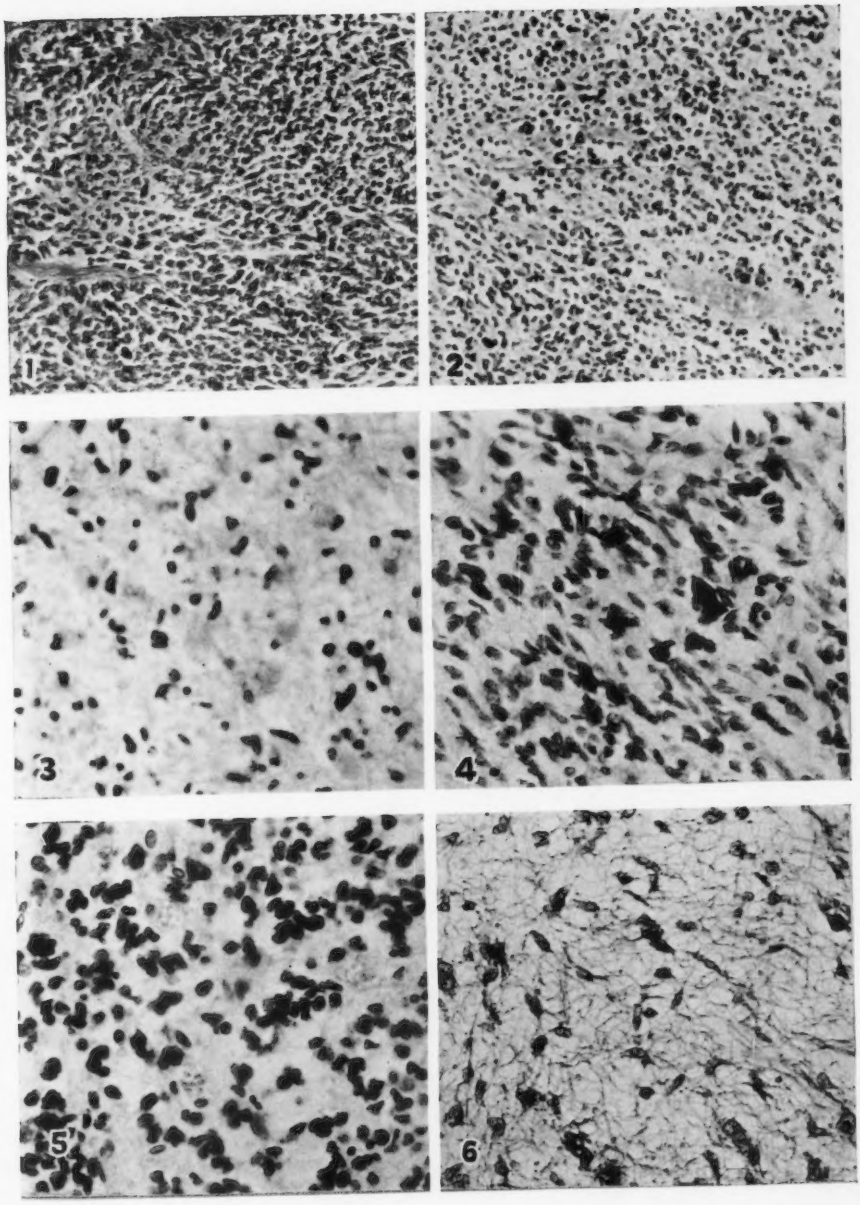
To illustrate paper by John E. A. O'Connell and Alexander Brunschwig.

PLATE X.



To illustrate paper by John E. A. O'Connell and Alexander Brunschwig.

PLATE XI.



To illustrate paper by John E. A. O'Connell and Alexander Brunschwig.

A CLINICAL STUDY OF THE RESPIRATORY MOVEMENTS IN HEMIPLEGIA.

BY LAWRENCE C. KOLB AND FRANÇOIS KLEYNTJENS.[1]

(From the Sub-Department of Neurology, the Johns Hopkins University, and the Medical Service of the Baltimore City Hospital.)

INTRODUCTION.

THAT the respiratory movements of the chest are modified on the hemiplegic side of the body has long been known, but the nature of these changes has been variously stated. Broadbent [2] noting, among other things, that respiratory movements still occurred on the hemiplegic side stated his theory of bilateral cortical representation of certain movements. Hughlings Jackson [10] declared that in cases of both early and late hemiplegia the respiratory movement of the thoracic cage is greater in quiet breathing on the affected side than on the normal side, but is of slightly less amplitude than it is on the normal side during deep voluntary inspiration. He further postulated that motor fibres pass directly from the cortex to the phrenic and costal centres of the cord controlling the respiratory muscles, while an inhibitory pathway exists between the cortex and the "superior respiratory centre" in the medulla.

Numerous writers [1, 11, 12, 13, 14, 15] state that the respiratory movements are decreased on the hemiplegic side. Grawitz [7] recorded kymographically the movements of both sides of the chest in thirty cases of hemiplegia, and found the excursion during quiet breathing was diminished in twenty-two. One case showed an increased expansion on the affected side which he ascribed to "crossed paralysis." Dejerine [5], after perimetric studies of the chest in inspiration and expiration, decided that the excursion is only diminished on the affected side in forced respiratory movements involving the accessory respiratory muscles. In ordinary breathing the amplitude is equal on both sides except in patients who being hemiplegic since childhood and having maldeveloped musculature show a decrease on the affected side.

Strümpell [19] stated that the diminished expansion on the affected

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side explains the observation that pulmonary disease is more often localized at the base on the affected side, and Faschingbauer [6] described clinical signs of basal atelectasis here.

Starr [18] declared that during coma and the period of shock inspection of the chest usually shows that the respiratory movements are more active on the paralysed side. On the other hand, Ross [16] described depression of respiration on the affected side in the first few days after the cerebral injury. The clinical study of a few cases suggested that the conflicting opinions might be clarified by a more careful graphic examination.

Methods.

An apparatus was constructed for simultaneously recording the movements of both sides of the chest. This consists of two small rubber balloons; each is connected by rubber tubing to a similar balloon stoppered into a bell jar. The bell jars in turn communicate with Marey tambours, the movements of which record on a kymograph. The free balloons are applied under a cardboard shell which is fastened to the chest by equal lengths of 2 in. adhesive tape extending from the posterior axillary line to just lateral to the costo-chondral junctions. A quantity of air is injected into these balloon systems which are connected by a cross piece of rubber tubing. This is then closed with a stop cock. The movements of the kymograph points are then checked by injecting 2 and 4 c.c. amounts of air into each system and measuring the deflections of the writing points on the kymograph. The time recorder was used in a few cases, but no additional information was obtained.

Kymographic tracings were obtained from three normal individuals, one case of pneumothorax, two cases of acute hemiplegia, fifteen cases of old hemiplegia, and one unilateral Parkinsonian syndrome. The cases of chronic hemiplegia are divisible into two groups: the first includes eight cases of spastic hemiplegia, while the second includes six cases of flaccid hemiplegia. The latter group consists of one case with a motor paralysis alone, and four with combined sensory-motor defects. A case of hemianesthesia without any motor defect is also included. This group is an unusual one and is intended to give no true significance as to the incidence of such cases. We were fortunate in being able to choose suitable patients from a series of over a hundred cases of hemiplegia in the chronic wards of the Baltimore City Hospital. Besides recording quiet respiratory movements and deep voluntary

inspirations, we also studied the effects of hyperpnœa induced by inhaling carbon dioxide in seven cases. Five other individuals were examined clinically, of these two were in deep coma and three had spastic hemiplegia.

Results.

As the findings in each group were constant, only the records from typical cases are presented here.

Case 1.—The first record (fig. 1) is that obtained from a healthy young individual. The tracing from the right side of the chest is placed below that on the left. The smaller waves are those during quiet respiration; the larger

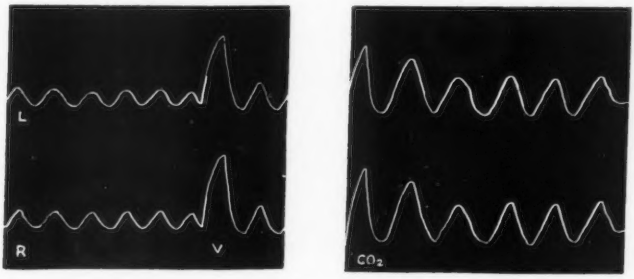

Fig. 1.—*Case* 1. Kymographic record of respiration of a normal individual. The upper record is that from the left side of the thorax, the lower from the right. On the left half of the record, the smaller waves are those of quiet respiration and the single large wave one of maximal inspiration. The tracings on the right were taken during hyperpnœa.

waves represent a single deep inspiration performed on command. To the right is a record from the same individual in hypernea following inhalation of carbon dioxide. Careful measurements with calipers show no variation in the size of the simultaneous movements of the two sides of the chest wall.

Case 2.—W. T. (J.H.H., U. 741716). The following case is an example of acute hemiplegia seven days after the cerebral lesion. This 33-year old negro was admitted to the hospital, complaining of shortness of breath and swelling of his ankles. He was treated as a case of rheumatic heart disease with aortic insufficiency and cardiac decompensation. Seven days after admission he suddenly became disorientated, and later became stuporous. The next day he had a flaccid paralysis of the left face, arm and leg. The respiratory tracing was taken six days later. The left side of the face was flattened, and he was unable to innervate the facial muscles, although the frontalis contracted bilaterally. The tongue deviated to the left. Both the left arm and leg lay flaccidly in extension and were hypotonic on passive movement. Sensation could not be tested, as he was still confused. The tendon reflexes in the arms were equal but sluggish. The left abdominal and cremasteric reflexes were

absent, and the left knee and ankle-jerk were less brisk than those on the right. No clonus was obtained. Hoffmann and Babinski signs were noted on the left.

The kymographic record (fig. 2) shows that the movements of the left side of the chest are diminished as compared with the normal right side. He was unable to execute voluntary expansion as he failed to understand commands; the arrows on the record indicate where such requests were made. However, in the tracings and observations made from the other cases of early hemiplegia voluntary movements were likewise diminished on the affected side.

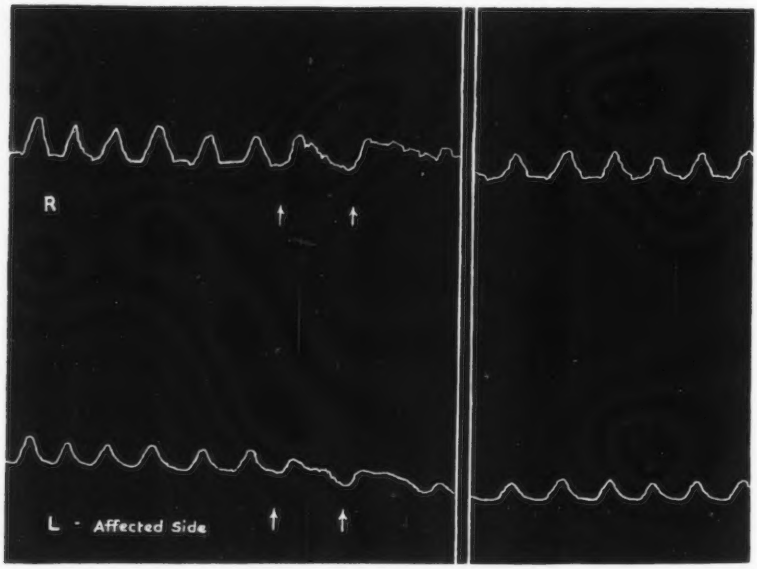

FIG. 2.—*Case* 2. Acute left hemiplegia seven days after cerebral accident. Right thorax recording above, left thorax below. Arrows indicate suggestions of voluntary inspiration not attempted by the patient.

Case 3.—H. R. (B.C.H., U. 19254). This case summarizes the findings in the group of spastic hemiplegics. A 40-year old negro ship's cook was admitted to the hospital complaining of left-sided paralysis of twenty years' duration. He had been struck on the head by a swinging door when his ship sank during the War, and on being carried off the vessel his left side was found to be paralysed. Since then his leg and arm have remained stiff and weak. The general physical examination was normal. On neurological examination the cranial nerves were normal, with the exception of a lower facial weakness and deviation of the tongue to the left. There was a marked spastic paralysis of the left arm and leg. The arm was carried adducted at the shoulder, flexed

to 70° at the elbow and flexed and pronated at the wrist. The muscles about the shoulder girdle were strongly contracted. This was particularly noted in the pectoralis major. The left rectus abdominis was more tense than the right. The left leg was maintained in 45° flexion at the hip and the same degree of flexion at the knee. Sensation was undisturbed. The tendon reflexes were all over-active on the left. The abdominal and cremasteric reflexes were not obtained and the Hoffmann and Babinski signs were present on the left. No clonus was noted.

On inspection of his chest, it was seen that both in normal and deep voluntary breathing the movements of the paretic side were decreased. This is borne out by the kymographic record (fig. 3). The second half of the record is that obtained following inhalation of carbon dioxide. At V_2 and V_3 are

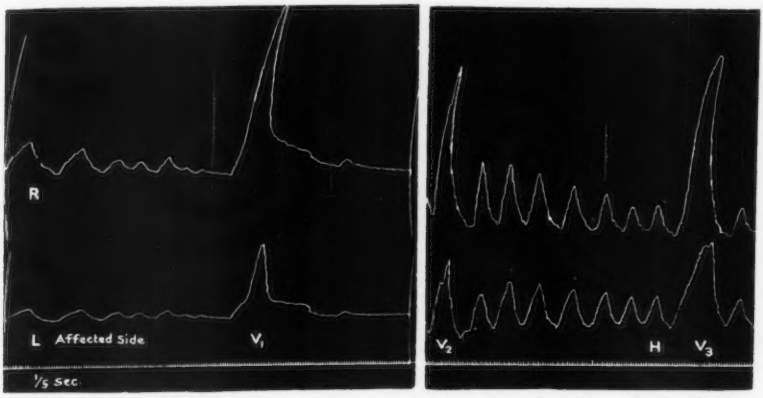

FIG. 3.—*Case* 3. Spastic left hemiplegia of twenty years' duration. Right chest recording above, left below. V_1, V_2, V_3, are voluntary inspirations. Right half of tracing records activity in hyperpnœa.

shown two voluntary inspirations. Between V_2 and V_3 we see the movements of the chest in hypernoea, and it is apparent that the amplitude is increased to a greater extent on the paralysed side than on the normal side. At H the inspiratory wave on the normal side measures only 1 cm. in the original, which is comparable to the waves during quiet respiration shown in the first part of the record. However, on the paretic side the amplitude is likewise 1 cm., an expansion never reached during quiet breathing. This increase in amplitude on the affected side is not true for attempted voluntary inspiration during the period of hyperpnœa. This was also observed in two other cases during study of hyperpnœa.

Case 4.—M. J. (B.C.H., 7999) presents a flaccid hemiplegia with no sensory changes whatsoever. He is the only case of this type examined. He is a 45-year old coloured male stevedore who came to the hospital complaining of shortness of breath and palpitation. He was treated as a case of rheumatic

heart disease with mitral insufficiency and decompensation. Seventeen days after his second admission in 1936 he woke in the morning and realized that his right face, arm and leg, were limp and useless. His condition gradually improved so that he was able to get around in a wheel chair.

A neurological examination was done four months after the onset of his paralysis at the same time the kymographic records were made. The cranial nerves were normal except for slight weakness of the masseter and pterygoid muscles on the right. The right side of the face was flattened and all movements of the muscles lost except wrinkling of the brow. The palate moved less rapidly on the right than the left and the tongue deviated to the right. The right trapezius and sternomastoid were weaker than those on the left.

There was complete loss of voluntary movement in the right arm and leg beyond the ability to raise the shoulder slightly and weakly flex and abduct

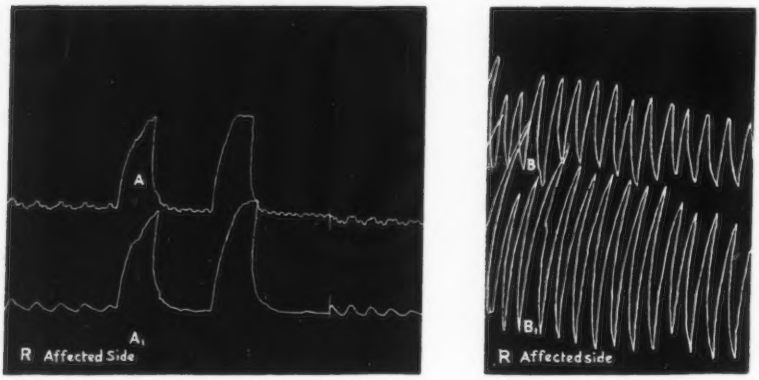

FIG. 4.—*Case* 4. Flaccid right hemiplegia of four months' duration. Left chest recording above and right below. Recording during hyperpnœa on the right half of the graph.

the thigh on the abdomen. The right arm lay flaccidly at his side. The right side of the chest moved with greater amplitude than the left in both quiet breathing and voluntary inspiration. The abdominal muscles were weaker on the right, and the leg on the same side was also hypotonic. There was atrophy of both the arm and thigh on the paretic side. No sensory changes were found. The tendon reflexes were equal but sluggish on both sides. A right Hoffmann but no Babinski response was obtained. The abdominal reflexes fatigued less easily on the left. He was diagnosed as a chronic flaccid motor hemiplegia.

On the left of the kymographic tracing (fig. 4) are presented the respiratory waves during quiet breathing and two waves of maximal voluntary inspiration. It is apparent that both are greater on the affected side. The cardiac apical impulse distorts the respiratory waves recorded from the left chest.

On the right side of the chart is presented the tracing obtained during

hyperpnœa. The greater amplitude on the affected side is striking. Again we notice that during hyperpnœa the amplitude of movement on the paretic side is increased out of proportion to that on the normal. This is made clearer if we compare the maximal voluntary inspiration on the normal side during quiet breathing with a wave of the same size during hyperpnœa, for instance A and B. Now if we compare the simultaneous waves on the affected side A_1 and B_1 we find that during hyperpnœa the wave on the paretic side is double that during voluntary breathing.

Case 5.—F. N. (B.C.H., U. 12693) has a hemianæsthesia with hypotonia, but no loss of motor power although movements are not performed with the usual facility on the affected side. He is a 60-year old white male labourer who was admitted to the hospital complaining of paralysis of the left arm and leg. Five years previously he suddenly suffered a tingling paræsthesia of the left arm and leg followed by weakness of the extremities, slight difficulty in

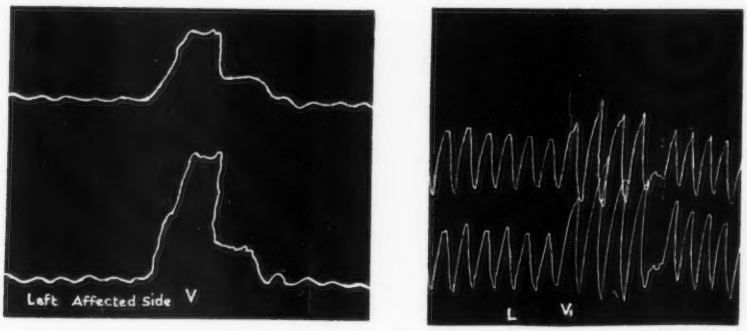

FIG. 5.—*Case* 5. Left hemianæsthesia of five years' duration. Right chest recording above, and left below. V_1 and V_2 indicate voluntary inspirations. Recording during hyperpnœa on the right.

speaking and urinary incontinence. He remained in bed, but on getting up seven weeks later had a similar seizure. Since then he has been unable to walk as he cannot support his weight on the left leg. He is, however, able to move both the arm and leg with considerable force. He has had several clonic convulsive seizures involving the left arm and leg since his admission. His general physical examination was normal except for considerable emphysema. The blood Wasserman and flocculation tests were reported as +4; the cerebrospinal fluid was clear and its Wasserman reaction negative.

The neurological examination, eight years after the onset of his illness, showed a fairly co-operative man, fatiguing easily, but in no distress. He was able to get about in a wheel chair. Over the left side of the head and face thermal, tactile, and painful sensations were greatly impaired and two-point sensation was lost. There was no loss of power in the muscles of mastication. The left facial muscles were hypotonic with flattening of the nasolabial

fold. Movements of these muscles were strong. The gag reflex was sluggish. The tongue was protruded to the left, but immediately afterward this position was corrected. The margins of the tongue were furrowed.

Examination of the motor system showed no weakness of any limb, but the muscles of the left arm and leg were hypotonic as evidenced by the subluxation present at all the joints on this side. This was so marked that dislocation of the shoulder could be easily produced either actively or passively. The muscles felt relaxed and showed a measurable atrophy.

Sense of passive movement and position, discrimination of Weber's compass points and deep pain sensation were lost over the whole left side. Tactile stimuli were appreciated over the face alone but only the extremes of hot and cold were felt elsewhere. These were often misstated. Painful stimuli were delayed and not very acute when felt.

The tendon reflexes were all equal and sluggish. There was no clonus, nor were Hoffmann or Babinski signs obtained. The abdominal reflexes were present in both superior quadrants but not in the inferior. There were no cremasteric reflexes.

The respiratory record (fig. 5) shows, as in the previous case, a larger amplitude of expansion on the affected side in both quiet and voluntary breathing. The increase on voluntary breathing is marked. In hyperpnœa, the amplitude of movement is not greatly increased on the affected side, although there is an increase in the amplitude of voluntary respiratory movements performed during this same period as shown at V_1.

Case 6.—M. D. (B.C.H., 12756) is representative for the group of four sensori-motor hemiplegics with flaccid palsies. This 52-year old coloured labourer came into the hospital in 1933, saying he had had a stroke. He was acutely ill. Temperature 103, pulse 90, respiration 20, blood-pressure 160/90. The chest expansion at this time was recorded as being limited on the left side. Percussion was normal, but auscultation revealed râles at the right base and axilla clearing after cough. There were signs of aortic insufficiency, but the rest of the general examination proved negative. On neurological examination there was paralysis of the face, arm and leg associated with a spasticity in the limbs, but the arm was carried in extension rather than in the usual flexed hemiplegic position. There was pitting œdema of both the left hand and leg. Sensation of tactile, thermal and painful stimuli were impaired over the whole extent of the left side of the body. Vibratory sensation, sense of passive motion and position and two point sensation were lost. Astereognosis was present on the left. The left biceps, triceps, supinator, knee and ankle-jerks were over-active, while the abdominal and cremasteric reflexes were diminished. There were a sustained wrist and an unsustained ankle clonus, but no Babinski or Hoffmann signs.

The urine, blood, and cerebrospinal fluid studies were normal, but the blood Wasserman and Kahn tests were reported as +4.

He continued to have painful pricking sensations over his left side, and at least on one occasion he felt an unusual sense of well-being in the same area.

On March 2, 1934, he had another "stroke" which increased the defect of movement in his arm and hand. His original spastic palsy now changed and with increasing flaccidity he had to take to a wheel chair. In August of 1936 it was noticed that he was running a remittent fever. On physical examination signs of a pleural effusion were present over the left lung base. Twice in October thoracentesis was performed and 800 c.c. of straw-coloured fluid was obtained. Fluid was still present by X-ray in September, 1936.

The neurological examination was repeated in September. He now appeared thin and emaciated, he was irritable but otherwise a good observer. The cranial nerves were essentially as reported before. He had no voluntary movement of the left extremity. There was atonia of all the musculature on the left side of the body with measurable atrophy of the arm and forearm, thigh and leg. The left arm lay flaccidly extended by the side, there was a

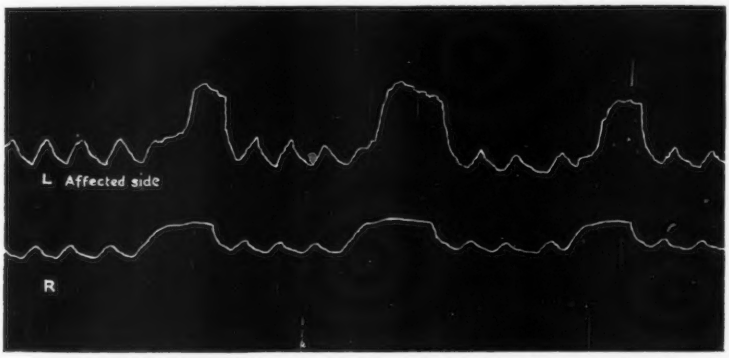

FIG. 6.—*Case* 6. Left flaccid sensori-motor hemiplegia. Left chest recording above and right below. Large waves are those of voluntary inspiration following command.

gap between the acromial tip and the head of the humerus. Subluxation was present at the left knee and ankle-joints and this limb lay flaccidly in a position of extension and external rotation. He pushed it about with his other foot. The sensory loss was extreme. Pain and the extremes of hot and cold, particularly the latter, gave rise to disagreeable sensations. Deep pain was delayed, but again often excessive. Vibratory impulses were dulled but when applied vigorously caused an intense boring feeling. The sense of passive movement showed the greatest disturbance in that even at the knee and elbows movement to 10° were not appreciated. The tendon reflexes remained increased on the left, with a sustained wrist clonus and an unsustained ankle clonus. There was no Babinski response or Hoffmann sign.

In December of 1936, with signs of pleural effusion still present in the left, the movements of his chest were recorded. It is evident that expansion is increased to a great degree, both in quiet and voluntary respiration at this time. There is thus an increase of movement on the flaccid hemiplegic side,

although an underlying pleural effusion might be expected to reverse the picture. It is of interest, also, that while the hemiplegia was spastic a note was made that the movements of the paretic side of the chest were decreased, whereas with flaccidity we record an increase on the same side. The observations and records obtained from the other three cases in this group also showed an increase in amplitude in both quiet and voluntary movement as well as during hyperpnœa (fig. 6).

Case 7.—L. R. (B.C.H., 17605). The following case is one of pulmonary tuberculosis with an artificial pneumothorax and is added as a contrast to the former as well as demonstrating the use of the apparatus in other pulmonary disorders. This 20 year old white boy was admitted to the hospital on

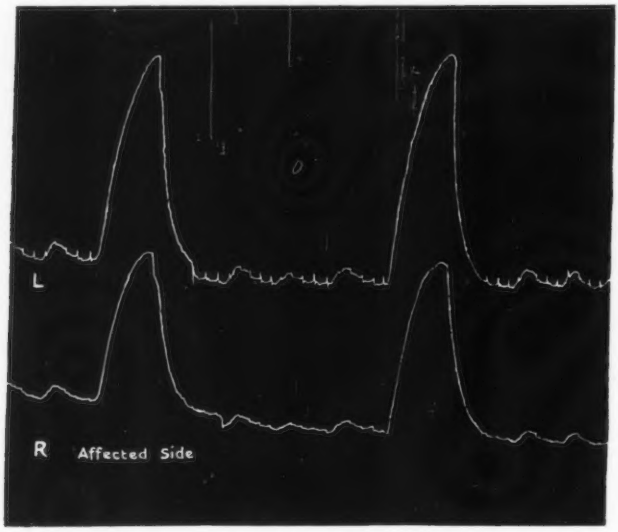

FIG. 7.—*Case* 7. Right pneumothorax therapy with refill one and a half hours previously. Left chest recording above and right below. Cardiac impulse shown distorting movements of left half of thorax.

December 1, 1936, stating that he had recently coughed blood on several occasions. On examination the right shoulder was carried slightly lower than the left, and the right clavicle was more prominent, due to some atrophy of the muscles here. There was a diminished excursion at this apex with decreased breath sounds anteriorly below the left clavicle. Over the right apex posteriorly the breath sounds were harsh and after cough a few crackling râles were heard. A Roentgenograph of the chest showed increased hilar shadows with infiltration extending towards the base and apices. He was started on pneumothorax therapy and had a 600 c.c. refill an hour and one half before the respiratory kymographic record was made.

The record (fig. 7) shows a decrease in quiet and voluntary respiration on the right side or the side of the pneumothorax. The record should be contrasted with that of the previous patient who showed an increased expansion on the paralysed side where he likewise had a pleural effusion.

Since the cases presented before suggest a relationship between spasticity and flaccidity and respiratory movements it seemed of interest to study a case of unilateral Parkinsonian syndrome. In this patient there was clear-cut rigidity on one side of the body although perhaps this rigidity cannot be directly compared with the spasticity seen in hemiplegia.

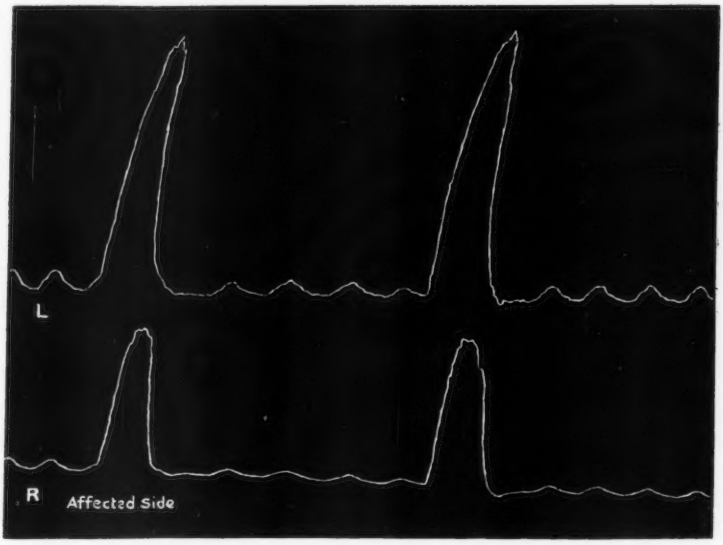

FIG. 8.—*Case* 8. Right hemi-Parkinsonian syndrome of nine months' duration. Left side recording above and right side recording below. Large waves are those of maximal voluntary inspiration.

Case 8.—(J.H.H., K. 99199). This 40 year old man showed the following neurologic abnormalities. His face was unusual in that the palpebral fissure was wider on the right and the facial muscles were immobile on that side. The right pupil was slightly larger than the left, but both reacted well to light and accommodation. The tongue was protruded to the right. There was a definitely increased rigidity to passive movements in the right arm and leg and a cog-wheel sensation was easily appreciated by passively flexing and extending the elbow. No tremor of the extremities was visible, but he had difficulty in fine movements of the right fingers. Sensation was undisturbed and the reflexes were within normal limits.

On inspection of his chest prior to recording the movements a slight lag was visible on the right side during maximal inspiration. The kymographic tracing (fig. 8) shows clearly the depression not only on voluntary inspiration but also during quiet respiration. The deflections of the writing point on the affected side are exactly one-half those on the normal throughout.

Discussion.

Most observations on this subject have been made by inspection and palpation of the chest alone, and in many instances no changes in respiration were observed. A study of our cases fails to confirm certain of the conclusions of previous clinicians which we summarized in the introduction. Our charts present certain graphic evidence concerning reflex activity in the presence of flaccidity or spasticity.

The records and observations indicate that shortly after the cerebral accident causing hemiplegia and while the patient is still in the period of reflex depression, the amplitude of movement on the affected side of the chest is diminished in both quiet and voluntary respiration. Starr's [18] statement that the movements were increased during this period might possibly be explained, if his patients were cyanotic, on the basis of a specific excitation of the respiratory centre during asphyxia such as we will discuss later. We have, however, examined two patients in this period in deep coma; one was cyanotic. In each case movement was definitely limited on the affected side. The paresis was so marked in the case showing cyanosis that the affected side of the chest was "sucked in" when expansion occurred on the normal side.

With spasticity such as occurs in long-standing cases of hemiplegia the same results are obtained: a diminution of expansion of the chest on the affected side during quiet breathing, voluntary respiration and hyperpnœa. This probably holds true for other states of rigidity as exemplified by our one case of unilateral Parkinsonism. On the contrary, with muscular hypotonia or flaccidity the amplitude of the respiratory movement is always greater on the affected side. An increase in excursion on the affected side has only previously been described by Jackson for quiet breathing and by Grawitz on his single case of "crossed paralysis." This is true no matter whether the hypotonia occurs with evidence of damage to the motor pathways alone, or sensory pathways or whether a combined motor-sensory loss is found.

It must be mentioned that the increase in movement on the affected side in flaccid hemiplegia is less easily determined on inspection of the

chest alone than in the cases of spastic hemiplegia. It occurs late in the act as a " lag " and is best seen in the first and second interspaces. It may be visualized better by standing behind the patient and becomes more apparent on placing the hands over the upper chest and comparing the movements of each hand during inspiration.

Although the observations have been few, the effects of hyperpnœa following inhalation of carbon dioxide, both in cases with spasticity and flaccidity, have shown that the increased depth of respiration persists for a longer period on the hemiplegic side than on the normal. In the cases of spacticity, at the end of the period of hyperpnœa the amplitude on the affected side may be equal to or greater than the normal side while formerly during quiet breathing it was always less. If a voluntary inspiration is taken during the period of hyperpnœa the amplitude of the movement is the same as that of voluntary inspiration during quiet respiration. Two possible explanations have occurred to us. Tone may be decreased during hyperpnœa, but if this is so we could expect an equal increase in amplitude on the normal side. This has never been true. The other is that pathways from the cortex or supra-medullary centres which control the activity of the respiratory centre in the medulla have been destroyed and this centre now acts alone and excessively.

Jackson originally suggested the existence of cortical inhibitory pathways because of the fact that quiet breathing was greater on the affected side while voluntary breathing was decreased. Although we have seen only one case showing such dissociation of amplitude between quiet and voluntary respiration movement, it does appear regularly in comparing reflex and voluntary breathing in hyperpnœa. Furthermore, the recent experimental work of Smith [17] and Bucy [4] corroborates the results of many previous workers who have demonstrated that arrest or slowing as well as acceleration of respiration can be produced by electrical stimulation of the cerebral cortex in man and animals.

Most writers have stated that the decrease of movement on the affected side occurs only in voluntary respiration. Nothnagel [13] and Strümpell [19] ascribed this to paralysis of the scalenus anticus muscle and they were later supported by Faschingbauer [6]. Our observation shows that this diminution occurs not only in voluntary respiration but also during quiet breathing. The question arises, are the intercostals paretic alone or is some other factor responsible for this change ? That movement occurs, though diminished in spasticity but increased in flaccidity, leads us to assume that the intercostal muscles are not

paralysed and that the variables of tone are responsible for the changes in amplitude.

The modifications of phasic reflex activity playing upon a background of tone has been described by Walshe [20] in his studies of the Babinski response in states of paraplegia in extension and paraplegia in flexion following spinal cord injuries. In the former the reaction may be a minimal dorsiflexion and abduction of the toe with dorsiflexion of the ankle and ham-string contraction, or as Walshe puts it, " the condition is one in which a flexion reflex incompletely overcomes a strongly maintained hypertonus in the antagonists." In the latter a flexor or mass reflex may supervene on a similar stimulus. In the first case the limb is spastic in extension and the withdrawal only momentarily overcomes the maintained over-active extensor reflexes, while in the latter this exaggerated antagonism is entirely removed and the movement is carried through to its completion.

Reflex respiration is modified in a similar way. It is apparent that voluntary movement likewise has its pattern changed by the existing tone of the portion of the body upon which it acts. It is difficult to separate the impairment of activity through loss of voluntary control from that caused by spasticity if one studies movements of the limbs. In the case of the thoracic cage we have a series of muscles receiving impulses from both hemispheres. If the efferent fibres from one cortex are totally destroyed, voluntary movement still occurs through ipsilateral impulses. This movement, voluntarily induced, must act on the hypertonic or hypotonic musculature affecting the chest wall. The present study presents graphically evidence of the fact that the manifestations of voluntary activity may be impeded or liberated when acting on a hypertonic or hypotonic musculature respectively.

The problem of spasticity leads one to consider what groups of respiratory muscles are hypertonic; whether the auxiliary muscles alone are concerned, or whether the intercostals are involved. In all our cases with spasticity the pectoralis major has formed a firm contracted mass holding the affected arm close to the chest. In several there was a palpable rigidity in the rectus abdominis on the affected side. An increased rigidity in the shoulder girdle and abdominal muscles alone would probably be capable of decreasing the excursion of the affected chest wall by holding the superior and inferior portions of the cage fixed.

In the absence of this spastic " brake " the movements become excessive. That such an event does occur is shown in our Case 6.

This patient was first seen with a spastic hemiplegia and noted as having a diminished expansion on the affected side. Later he developed a flaccid paralysis after a second cerebral accident and now shows an increased excursion on the affected side.

The interaction of the various muscle groups is still obscure. Hoover [8, 9] and Briscoe [3] have described in detail the actions and integrations of the auxiliary muscles with the intercostals and diaphragm in modifying movements of the chest wall. More detailed study with a clearer knowledge of these normal interactions is necessary to explain fully the changes described here.

Summary.

(1) A method is described of recording with a kymograph the simultaneous movements of both sides of the chest.

(2) These movements have been studied in twenty-one cases, including three normal individuals, one case with a pneumothorax, three cases of early hemiplegia, eight cases of spastic hemiplegia, five cases of flaccid hemiplegia, one case of hemianæsthesia and one case of unilateral Parkinsonism.

(3) Normal respiratory activity and movements induced voluntarily were found always diminished on the affected side in acute hemiplegia and in chronic spastic hemiplegia.

(4) Normal respiratory activity and movements induced voluntarily were found always increased on the affected side in chronic flaccid hemiplegia and in one case of hemianæsthesia.

(5) During hyperpnœa the movements on the affected side are increased out of proportion to those on the normal side. This increase persists longer than on the normal side and is noted in both spastic and flaccid hemiplegia.

(6) In one case of unilateral Parkinsonism both reflex respiration and voluntary respiratory movements were decreased on the affected side.

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Notices of Recent Publications.

Handbuch der Neurologie. Herausgegeben von O. Bumke und O. Foerster. Berlin: J. Springer. 1936 and 1937.

The four volumes referred to below complete the System of Neurology which has been compiled under the direction of Professors Bumke and Foerster, who deserve the gratitude and congratulation of neurologists on the successful accomplishment of their enormous task. As a work of reference it will be invaluable; the provision of a general index to the eighteen volumes would, however, make it even more useful.

Band II. *Experimentelle Physiologie.* S. 561, mit 137 Abbildungen. Price RM. 105.

The inclusion of this volume indicates the wide scope on which the "Handbuch" was planned. The physiology and mechanics of muscular activity, the physiology of the vegetative system and the conditioned reflexes are dealt with in addition to the functions of the central nervous system. The most noteworthy chapters are perhaps those on the spinal cord by Brücke, on the brain-stem by Rademaker, and on the physiology of the cerebellum and of the cerebral cortex by Dusser de Barenne, but all contributions to it will be of interest to neurologists. Though written as a symposium of the experimental physiology of the nervous system the volume would have been of greater service to the clinician if it had been planned with more immediate reference to the practical or clinical significance of facts and hypotheses which have resulted from experimental work; it is for instance disappointing to find in Berger's chapter on the physiological accompaniments of psychical activity only a page devoted to electric potentials of the brain, while the reader will search in vain for an account of the nervous control of the bladder and rectum. It seems, too, that a few of the authors were more anxious to present their personal views rather than give a general review such as a book as this demands.

Band III. *Quergestreifte Muskulatur, Rückenmarksnerven, Sensibilität, Elektrodiagnostik.* S. 1128, mit 851 Abbildungen. Price RM. 236.

The first half of this volume is devoted by Foerster to the physiology and functional pathology of the striated muscles. The primary and secondary actions of each muscle, and the mechanism of movement at each joint, are fully described, as well as the effects both in rest and in movement of palsies

of the individual muscles. The treatment of muscular paralysis, especially by substitution operations, is included. The chapter is a uniquely comprehensive contribution to an important subject, details of which are often neglected. F. Kramer deals with the symptoms of injury and disease of the somatic nerves and plexuses.

Another short but extremely valuable chapter is contributed by v. Weizsäcker on the examination of sensation. In addition to the methods and principles of examination he analyses the various qualities and functions of sensation, and discusses the physiological and psychological factors which may influence the phenomena that result from sensory disturbances. Altenburger's chapter on electrical diagnosis, including chronaxie and the study of action currents in normal and pathological conditions, extends to 340 pages; the significance of the facts revealed by these methods of electrical investigation are analysed and discussed.

Band XV. *Endokrine Störungen.* S. 469, mit 46 Abbildungen. Price RM. 88.

This volume on disturbance of the ductless glands has been wholly written by A. Jores and M. Nothmann, who have evidently collaborated closely in its production. Some of the chapters, as those on the hypophysis-hypothalamic system and the epiphysis, are of direct concern to the neurologist, but many of the others have only an indirect interest, but the volume will be welcome as an up-to-date exposition of subjects which are assuming more and more importance in all branches of medicine.

Band XVI. *Angeborene, Früh Erworbene und Heredo-Familiäre Erkrankungen.* S. 1172, mit 442 Abbildungen. Price RM. 228.

Probably no more difficult task lies before the author who writes on nervous diseases than to classify and describe the various hereditary and familial affections, for often their pathology and symptoms vary in different families, and many cases fail to fall into classical types. How important the hereditary factor may be in pathogenesis is sometimes disputable, for instance, in this volume progressive muscular atrophy, amyotrophic lateral sclerosis, syringomyelia, paralysis agitans and myasthenia gravis are, contrary perhaps to the experience of most, placed among the hereditary diseases or attributed to hereditary influences. But this is only a matter of arrangement, and the juxtaposition of the myopathies to other affections in which muscular wasting is the most prominent symptom, and of paralysis agitans to hereditary diseases characterized by involuntary movements, certainly makes for convenience. All the hereditary affections are fully described and well illustrated, and, as in the volumes, the numerous references and the extensive bibliographies will be extremely useful. The volume also contains chapters on congenital defects and on affections dating from birth or infancy, as Wohlwill's excellent article on the cerebral hemiplegias, diplegias and allied conditions. Hereditary affections of the eye and ear, which neurologists often meet, are also described.

Précis d'Anatomo-Physiologie Normale et Pathologique du Système Nerveux Central. Par P. MASQUIN et J. O. TRELLES (sous la direction de Jean Lhermitte). Paris: G. Doin et Cie. 1937. Pp. 613, avec 185 figures. Price 165 Fr.

Of the many praiseworthy attempts in recent years to provide the student of neurology with a résumé of the more important facts of anatomy and physiology on which to base clinical study none perhaps has been so pretentious and on the whole so successful as this volume written under the supervision of Professor Lhermitte. Its authors start with the assumption that in the study of the nervous system physiology is inseparable from anatomy, while a knowledge of the phylogenetic evolution of structure is often necessary for the proper comprehension of function. Consequently they introduce the chapters on each division of the nervous system by a short sketch of its ontogeny, and often refer to its comparative development; its anatomy and connections are then described and its main functions and the effects of their disturbances are discussed. On the whole this method has yielded excellent results and has furnished the student with an adequate foundation for clinical work, but, as is perhaps inevitable in such a task, the authors have in many cases failed to hold fairly the balance between condensation and completeness, more particularly in the matter of exclusion or introduction of discussions on function, but in this question there is obviously room for diverse opinions. There can be no doubt, however, on the success which the authors have achieved, or on the utility of this book. Some of the diagrams are open to adverse criticism; many are so crude and so unlike the structures they represent that the student may have difficulty in transferring what he learns from them to the anatomy he already knows or studies, and yet many are not so clear as to justify the simplification which is attempted. The extensive use of eponymous terms, always popular in France, is another drawback for the English reader, but the provision of an excellent index is a praiseworthy feature of the volume.

Études sur le Spina Bifida. Par J. LEVEUF (avec la collaboration de I. BERTRAND et H. STERNBERG). Paris: Masson et Cie. 1937. Pp. 330, avec 176 figures. Price 75 Fr.

This volume may safely claim to become a classic in the literature of spina bifida and allied conditions. It is comprehensive yet concise, clearly written and admirably illustrated. The developmental errors to which spina bifida is due are dealt with by Dr. Sternberg of Vienna, and Dr. Bertrand describes the malformations of the brain and cord often associated with it, but the main part is written by Professor Leveuf, who gives in an appendix records of eighty cases which he has observed.

The more important features of the volume are a careful study of the

meninges in spina bifida, which enables him to trace the neuro-ectodermal origin of the pia-arachnoid, and the descriptions of mild forms of meningocele which are related to the fully developed forms of the condition. Ætiological factors, in which syphilis is regarded as important, and the various complications are fully discussed. The treatment of spina bifida and the immediate and later results of operation are also dealt with on the basis of the author's large personal experience. The publishers deserve congratulation on the excellent reproduction of the illustrations.

Lehrbuch der Nervenkrankheiten. VON R. BING. 5te Aufl. Berlin: Urban und Schwarzenberg. 1937. S. 618, mit 207 Abbildungen. Price RM. 25.

After an interval of less than five years the author of this useful textbook was called on to provide a new edition, which appears in essentially the same form, but with an addition of 50 pages which are distributed over several of the chapters. The book still preserves its predominantly clinical character, but due attention is given to the pathogenesis and morbid anatomy of disease and to the origin and significance of symptoms. To students and practitioners who read German it can be strongly recommended; to others an English translation of this edition would be welcome.

Les Maladies Nerveuses. Par A. VAN GEHUCHTEN. 4me Édition. Louvain: Libraire Universitaire. 1936. Pp. 718.

The fourth edition of van Gehuchten's textbook has been brought up to date and enlarged by his son and successor, but the general plan is that of the original author. It is claimed to be a simple and practical presentation of clinical neurology with adequate reference to pathology, and such it is. There are numerous illustrations, but unfortunately many are not well chosen or satisfactorily reproduced.

Le Tonus des Muscles Striés. Par G. MARINESCO, N. JONESCO-SISESTI, O. SAGER et A. KREINDLER. Preface de Sir Charles Sherrington. Imprimerie Nationale, Bucarest. 1937. Pp. 355.

A short but delightful preface from the pen of Sir Charles Sherrington introduces this comprehensive and valuable monograph. It opens with a critical review of all the experimental data now available upon the problem of skeletal muscle tonus, and thus gathers together a vast mass of information in concise and lucid manner. The application of this knowledge to the clinical study of motor disorders, and the additions thereto which clinical investigation has made possible are then fully described. The symptom-complexes of pyramidal and extrapyramidal disorders are analysed on physiological principles, utilizing the work of Sherrington, of the Utrecht school and of Lapicque.

Much original work of the authors is also included. This is the first satisfactory approach to a synthesis of the experimental and clinical work upon the problem of muscular tonus, and it may be warmly commended to all who are interested in this problem.

Die Hirnkammerformen bei Hirntumoren. VON OTTO DYES. Leipzig: G. Thieme. 1937. S. 79, mit 105 Abbildungen. Price RM. 16.

This monograph on the interpretation of encephalograms in cases of cerebral tumour is so profusely illustrated that it may be described as an atlas. The 105 figures which it contains will, apart from the text, be found extremely useful, and the discussions on the reading of films and the significance of details, many often lost sight of, adds to its value. The numerous radiograms are excellently reproduced.

Abcès subaigus et chroniques des hémisphères cérébraux : Sur une méthode de traitement. Par CLOVIS VINCENT, MARCEL DAVID et HARDEN ASKENASY. Paris: Masson et Cie. 1937. Pp. 46.

The authors describe a method they have employed successfully in the treatment of chronic or subacute cerebral abscess. The method of choice, when the abscess wall is sufficiently thick, is the ablation of the entire abscess with its surrounding brain. When this is not immediately possible a preliminary decompression over the abscess is performed, leaving the dura intact. A suitable moment for ablation is then awaited, and pending it aspiration of the abscess may be necessary.

Over de Diagnostiek van Het Meningioma Cerebri. door A. C. DE VET. Scheltema and Holkema, Amsterdam. 1936.

In this University Thesis the author records the analysis of the history and symptoms of a series of thirty-eight cases of cerebral endothelioma, undertaken to discover if possible any indications by which a pathological diagnosis of the nature of the growth can be made clinically, and for the guidance of the surgeon.

He finds no constantly present or pathognomonic sign by which the presence of an endothelioma can be ascertained before operation. Nevertheless a number of interesting points emerge from the study. When "irritative" symptoms, i.e. Jacksonian attacks, occur in cases of parasagittal endothelioma, the cortical point of origin of the attack as revealed by its form is likely to be related to the periphery rather than to the centre of the growth as this is viewed from the surface. Homolateral paresis and reflex changes are occasionally seen and are presumably due to pressure of the edge of the tentorium upon the laterally displaced cerebral peduncle, as originally described by Kernohan and Woltman. This "false localizing sign" seems commonly

associated with frontal endothelioma. Another common feature of endothelioma is a fluctuation of symptoms in its clinical course.

Radiological examination frequently reveals either rarefaction or thickening of the skull overlying an endothelioma. The various appearances in the latter case are described. The presence of calcification in the tumour substance was exceptional. Ventriculography was of no considerable assistance, and is in the author's view to be avoided when adequate localizing information can be otherwise obtained.

Études Neurologiques. Par G. GUILLAIN et P. MOLLARET. Paris: Masson et Cie. 1936. Pp. 300. Price 60 Fr.

The present is the seventh volume of the series. It contains a lengthy study of Friedreich's Ataxy, with particular reference to the bulbo-cardiac syndrome which frequently heralds a fatal termination of the malady. Other chapters deal with the myoclonic syndrome and with a variety of neuropathological problems.

The material is presented in the attractive and lucid manner which readers of the series have learned to expect.

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EDITOR.